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METABOLISM

AND

PRACTICAL MEDICINE

BY

CARL VON NOORDEN

PROFESSOR OF THE FIRST UNIVERSITY MEDICAL CLINIC, VIENNA

VOL. III.—THE PATHOLOGY OF METABOLISM

BY

CARL VON NOORDEN, H. SALOMON, A. SCHMIDT, A. CZERNY,
H. STEINITZ, C. DAPPER, M. MATTHES, C. NEUBERG,
O. LOEWI, AND L. MOHR

ENGLISH ISSUE UNDER THE EDITORSHIP OF

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PROFESSOR OF PATHOLOGY, UNIVERSITY COLLEGE, BRISTOL; PATHOLOGIST
TO THE BRISTOL ROYAL INFIRMARY

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1907

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PREFACE TO VOL. III.

Special efforts have been made in order to issue this third volume at an early date. While, however, it appears almost simultaneously with the German edition, it has been subject to considerable revision. Recent English, American, and Continental work has been added to the text and bibliography, and several sections have been partially rewritten.

The subjects dealt with are those of particular interest to the specialist and the practitioner, and they are accordingly considered in greater detail than was permissible in the preceding volumes.

It was felt than an Appendix containing the analysis and calorific values of the commoner foods would make the book more useful in everyday practice. Such has therefore been prepared specially for this English edition, the values for cooked as well as for uncooked foods being calculated for the English as well as for the metric system of weights.

I have to thank each of the translators for their assistance, and for the interest they have manifested during the preparation of the work. To Professor Halliburton, Dr. F. W. Mott, Dr. E. I. Spriggs, and others, I am indebted for much information on certain subjects.

I. WALKER HALL.

Bristol,
August, 1907.

CONTENTS OF VOL. III.

CHAPTER		PAGE
I.	Diabetes Mellitus. *By Carl von Noorden*	527
	I. Pathogenesis of Glycosuria	528
	A.—Renal Diabetes	529
	B.—Hyperglycæmia	532
	C.—Causes of Hyperglycæmia	535
	D.—Diabetic Hyperglycæmia and Glycosuria	542
	E.—Pancreatic Diabetes	560
	F.—Suprarenal Diabetes	564
	G.—Acromegaly Diabetes	565
	II. Energy Exchange	566
	III. Protein Metabolism	569
	IV. Carbohydrates of Diabetic Urine	571
	V. Acetone and Allied Bodies—Coma	586
	VI. The Urine in Diabetes	602
	VII. The Blood in Diabetes	614
	VIII. The Digestive Organs in Diabetes	621
	Literature	627
II.	Gout. *By Carl von Noorden*	646
	I. Transformation of Energy	646
	II. Metabolism of Protein	647
	III. The Digestive Organs	651
	IV. Uric Acid	655
	V. The Blood	678
	VI. The Urine	680
	VII. Theories	685
	Literature	687
III.	Obesity. *By Carl von Noorden*	693
	I. Energy Exchange	693
	II. Metabolism of Protein	703
	III. The Digestive Organs	704
	IV. The Blood	706
	V. The Urine	708
	Literature	714

CHAPTER PAGE

IV. Rarer Derangements of Carbohydrate Metabolism. *By Carl Neuberg* - - - - - - 716

I. Fructosuria (Lævulosuria) - - - - 716
II. Pentosuria - - - - - - 722
III. Glycuronic Acid—Characters and Excretion - 727
IV. Lactosuria - - - - - 737
V. Maltosuria - - - - - - 741
VI. Cane-Sugar and Iso-Maltose - - - - 742
VII. Inosituria - - - - - - 743

V. Diseases of the Skin. *By Salomon and von Noorden* - - 745

I. Nutrition and Energy Exchange - - - 745
II. Sweat and Dermatoses - - - - 750
III. Metabolism of Albumin - - - - 753
IV. Digestive Disorders in Skin Diseases - - 755
V. The Urine in Skin Diseases - - - - 761
VI. The Blood in Skin Diseases - - - - 765
VII. The Kidneys in Skin Diseases - - - 776
VIII. Diabetes and Skin Diseases - - - - 779
IX. Gout and Skin Diseases - - - - 782
X. Chemical Changes in the Skin - - - 783

VI. Cancer. *By A. Schmidt* - - - - - - 797

I. Influence upon Digestive Processes - - 798
II. Influence upon the Blood - - - - 805
III. Influence upon Nutrition and Protein Disintegration - - - - - - - 811
IV. Influence upon the Urine - - - - 815
V. Specific Action on Metabolism - - - 820
Addendum - - - - - 824

VII. Children's Diseases. *By Czerny and Steinitz* - - - 833

I. Composition of the Child's Tissues - - - 834
II. Gastro-intestinal Processes - - - - 837
A.—Food - - - - - - 837
B.—Saliva - - - - - - 838
C.—Gastric Processes - - - - 838
D.—Intestinal Processes - - - - 843
E.—Toxines—Detoxication - - - - 850

III. Absorption - - - - - - 852
A.—Protein - - - - - - 852
B.—Fat - - - - - - 856
C.—Carbohydrates - - - - - 857
D.—Mineral Matter - - - - 859

CHAPTER PAGE

VIII. Mineral Waters and Metabolism. *By von Noorden and Dapper* - - - - - - - 897

I. Energy Exchange - - - - - 899
II. Protein Metabolism - - - - - 901
III. Influences of Mineral Waters on the Stomach - 904

A.—Changes in Molecular Concentration - 904
B.—Action on Time of Digestion - - 908

IV. Influence of Mineral Waters on the Intestine - 918

A.—Assimilation of Food-stuffs - - - 919
B.—Bacterial Decomposition - - - 923

V. Influence of Mineral Waters on the Blood - 929

A.—Concentration of the Blood - - - 929
B.—Molecular Concentration of the Blood - 931
C.—Hæmopoiesis - - - - - 934
D.—Alkalinity - - - - - 937

VI. Influence of Mineral Waters on the Urine - 941

A.—Diuresis and Excretion of Salts - - 941
B.—Reaction of the Urine - - - 944
C.—Nitrogenous Substances - - - 948
D.—Non-nitrogenous Substances - - - 954

Literature - - - - - 956

IX. Baths and Metabolism. *By Max Matthes* - - - 958

1. Cold Baths - - - - - - - 958
2. Hot Baths - - - - - - - 965
3. Tepid Baths - - - - - - - 971
4. Mechanical or Chemical Stimulation - - - 971
5. Effect on the Secretions - - - - - 975
6. Local Effects - - - - - - 977
7. Action on Blood - - - - - - 978

X. Ductless Glands. *By A. Magnus-Levy* - - - - 983

I. Thyroid Gland Diseases - - - - 983

A.—Myxœdema - - - - - 983
B.—Thyroid Administration - - - 991
C.—Graves' Disease - - - - 995
D.—Thyroid and Carbohydrate Metabolism - 1003
E.—Theory of Action of Thyroid Gland - 1005

II. Acromegaly - - - - - - 1017
III. Addison's Disease - - - - - 1019

CHAPTER PAGE

XI. The Rarer Disturbances of Protein Metabolism. *By Carl Neuberg* - - - - - - 1021

I. Cystinuria - - - - - - 1021
II. Excretion of Diamines - - - - 1032
III. Alkaptonuria - - - - - - 1036

XII. Oxaluria. *By Carl Neuberg* - - - - - 1046

1. General - - - - - - - 1046
2. Occurrence - - - - - - - 1046
3. Origin - - - - - - - 1048
4. Treatment - - - - - - - 1052

XIII. Phosphaturia. *By Carl Neuberg* - - - - - 1055

1. Physiological - - - - - - 1056
2. Nervous - - - - - - - 1057
3. Sexual - - - - - - - 1058
4. Juvenile - - - - - - - 1058

XIV. Drugs and Poisons: Influence on Metabolism. *By Otto Loewi* - 1061

I. Water and Neutral Salts - - - - 1062
Iodides and Bromides - - - - 1064
II. Acids - - - - - - - 1066
III. Alkalis - - - - - - - 1070
IV. Boric Acid and Borax - - - - - 1083
V. Poisons producing Symptoms Characteristic of Want of Oxygen - - - - - 1084

A.—Blood Poisons - - - - - 1085

1. Carbon Monoxide - - - 1086
2. Other Blood Poisons - - - 1095

B.—Poisons affecting Respiration - - 1098
C.—Poisons affecting Cell Oxidations - - 1101

1. Prussic Acid - - - - 1101
2. Phosphorus, Halogen, Narcotics of Fatty Series, Arsenic, Antimony, Iron - - - - - 1107

D.—Mercury - - - - - 1141
Uranium - - - - - 1143
Chromium, Cantharides, Lead, Platinum, Copper, Zinc - - - - 1144

VI. Narcotics and Hypnotics - - - - 1146

1. Chloroform, Chloral Hydrate, Chloralose - 1148
2. Ether and Paraldehyde - - - 1152

CHAPTER PAGE

Drugs and Poisons (*continued*):

3-6. Amylene Hydrate, Sulphonal, Trional, Urethane, Veronal - - - - - 1152

7. Morphine Group - - - - - - 1153

8. Alcohol - - - - - - - 1153

VII. Antipyrin - - - - - - - 1157

VIII. Antifebrin, Thallin, Kairin - - - - 1162

IX. Quinine - - - - - - - 1164

X. The Salicylic Acid Group - - - - 1172

1. Salicylic Acid and Salicylates - - 1172

2. Benzoic and Gallic Acids - - - 1173

3. Phenol - - - - - - 1174

XI. Caffeine - - - - - - - 1175

XII. Cocaine - - - - - - - 1177

XIII. Pilocarpine - - - - - - 1177

XIV. Atropine - - - - - - - 1179

XV. Curare - - - - - - - 1180

XVI. Adrenalin - - - - - - 1181

XVII. Phlorizin - - - - - - - 1183

XV. Influence of Light on Metabolism. *By Hugo Salomon* - - 1199

1. Penetrating Power of Light - - - - 1199

2. Influence on Development and Cell Life - - 1201

3. Influence on Motor Processes - - - - 1205

4. Effect on Oxidation - - - - - 1206

5. Action on Enzymes - - - - - - 1212

6. Effect on the Blood - - - - - 1212

7. Protein Metabolism - - - - - 1214

8. Digestion - - - - - - - 1214

9. Effect on the Skin - - - - - 1214

10. Sensitization - - - - - - 1215

Röntgen and Radium Rays - - - - - 1220

1. Penetrating Power - - - - - - 1220

2. Influence on Cell Life - - - - - 1220

3. Influence on Motor Processes - - - - 1222

4. Influence on General Nutrition - - - 1222

5. Action on Fermentation - - - - - 1222

6. Effect on the Blood - - - - - 1224

7. Protein Metabolism - - - - - 1229

8. Action on Digestion - - - - - 1232

9-11. Action on Glandular Organs - - - - 1233

12. Action on Skin - - - - - - 1234

Literature - - - - - - 1234

CHAPTER PAGE

XVI. Nervous and Mental Diseases. *By L. Mohr* - - - 1243

A.—Energy Exchange - - - - - 1244
B.—Protein Metabolism - - - - - 1247
C.—Metabolism of Phosphorus - - - - 1250
D.—Carbohydrate Metabolism - - - - 1251
E.—Digestive Organs - - - - - - 1252
F.—Blood - - - - - - - 1253
G.—Cerebro-spinal Fluid - - - - - 1254
H.—Urine - - - - - - - 1255

Literature - - - - - - 1256

XVII. Bone and Joint Diseases. *By L. Mohr* - - - - 1261
Pathogenesis - - - - - - - 1273

XVIII. Diabetes Insipidus. *By L. Mohr* - - - - - 1279

Appendix: Analysis and Calorific Values of the Commoner Foodstuffs. *By Katharine L. Williams* - - - - - 1290

Index to Vols. II. and III. - - - - - - 1299

LITERATURE

The following abbreviations are used throughout:

A. C.	Annali di Chimica.
A. c. p.	Annales de Chimie et de physique.
A. C.-Z.	Allgemeine medicinische Central-Zeitung.
A. D.	Arbeiten des pharmakologischen Inst. zu Dorpat.
A. D. S.	Annales de Dermatologie et de Syphilologie.
A. F.	Archivio di Farmacologia e Terapeutica.
A. F. s.	Archivio di Farmacologia sper.
A. H.	Archiv der Heilkunde.
A. i. B.	Archives italiennes de Biologie.
A. J. M. S.	American Journal of the Medical Sciences.
A. J. O.	American Journal of Obstetrics.
A. J. P.	American Journal of Physiology.
A. J. U.	American Journal of Urology.
A. K.	Arbeiten aus der städtischen Krankenh. zu Frankfurt-a-Main.
A. k. G.	Arbeiten aus dem kaiserl. Gesundheitsamte.
A. L. I.	Arbeiten aus dem Leipzig physiolog. Institut.
A. M.	Archives of Medicine (New York).
A. P.	Anat. physiol. Untersuchungen (Wien).
A. p. H.	Archiv für physiologische Heilkunde.
A. Ph.	Archivio di Pharmakoterap.
A. S. B. / A. s. b.	Archives de Sciences biologiques, St. Petersb.
A. T. S.	Archiv für Tropen und Schiffshagg.
Ac. T.	Accademia medica di Torini.
An. c. F.	Annali di Chimica e di Farmacologia.
An. c. P.	Annalen der Chemie und Pharmacologie.
An. g.-u.	Annales des Maladies des organes génito-urinaires.
An. gy.	Annales de gynécologie.
An. hy.	Annales d'hygiène publique.
An. I.	Annali d'Igiene sperimentale.
An. m.-p.	Annales médico-psychologiques.
An. P.	Annales de l'Institut Pasteur.
An. S.	Annals of Surgery.
An. S. K.	Ann. Städt. Allg. Krankenh. (München).
An. T.	Annales de Thérap. dermat. et syphil.
An. u.	Annales univ. de Méd. et Chirurgie.
Ar. A. P.	Archiv für Anatomie und Physiologie.
Ar. B.	Boas's Archiv.
Ar. c. B.	Archives cliniques de Bordeaux.
Ar. D. S.	Archiv für Dermatologie und Syphil.
Ar. E. O.	Archiv für Entwickelungsmech. der Organismen.

Ar. F.	Archivio di Fisiologia.
Ar. g. m.	Archives générales de Médecine.
Ar. Gy.	Archiv für Gynäkologie.
Ar. H.	Archiv für Heilkunde.
Ar. h. B.	Archiv für die holländischen Beitr. z. Natur.- und Heilkunde.
Ar. Hy.	Archiv für Hygiene.
Ar. i. B.	Archives italiennes de Biologie.
Ar. i. M.	Archivio italiano di Clinica Medica.
Ar. i. P.	Archives internat. de Pharmac. et de Thérap.
Ar. K.	Archiv für Kinderheilkunde.
Ar. k. C.	Archiv für klinische Chirurgie (Langenbeck's).
Ar. M.	Archiv für klinische Medicin.
Ar. m. A.	Archiv für mikroscop. Anatomie.
Ar. m. ex.	Archives de médecine expérimentale.
Ar. n.	Archives de Névrologie.
Ar. p. A.	Archiv für patholog. Anat. und Physiol. (Virchow).
Ar. P.	Archives de Physiologie.
Ar. P. M.	Archiv für die gesammte Physiol. des Menschen (Pflüger's).
Ar. P. N.	Archiv für Psychiatrie und Nervenkrankh.
Ar. P. P.	Archiv für exper. Pathologie und Pharmakologie.
Ar. Ped.	Archives of Pediatrics.
Ar. Ph.	Archives of Physiology.
Ar. R. R.	Archives of the Roentgen Ray.
Ar. S.	Archives of Surgery.
Ar. S. M.	Archivio per le Scienze mediche.
Ar. s. p.	Archives des Sciences physiques et naturelles.
Ar. T.	Archiv für wissenschaftliche und prak. Tierheilk.
Ar. V.	Archiv für Verdauungskrankheiten.
Arb. M.	Arbeiten aus dem med.-klin. Inst. zu München.
B. A.	Berlin Akademy.
B. A. P.	Beiträge zur Anat. und Physiologie.
B. B.	Berichte der Bayer. Akad. der Wissen.
B. C.	Biologisches Centralblatt.
B. C. G.	Berichte aus der Chemische Gesell.
B. d.	Berichte der deutsche pharm. Gesell.
B. D. N.	Berichte der Dorpater Naturforsch. Gesell.
B. J.	Biochemical Journal.
B. J. C. D.	British Journal of Children's Diseases.
B. J. D.	British Journal of Dermatology.
B. K.	Berliner Klinik. Sammlung klin. Vorträge.
B. K. T.	Beiträge zur Klinik der Tuberkulose.
B. k. W.	Berliner klinische Wochenschrift.
B. M. J.	British Medical Journal.
B. M. R.	Birmingham Medical Review.
B. M. & S. J.	Boston Medical and Surgical Journal.
B. M. v.	Bulletin de la Soc. centr. de Méd. vét.
B. p. G.	Berlin phys. Gesellschaft.
B. roy. M.	Bulletin de l'Académie roy. de Médecine.
B S. A.	Berichte der Sächs' Akademy.
B. S. P.	Bulletins et Mémoires de la Soc. anat. de Paris.
Be. A. P.	Beiträge zur pathol. Anat. (Zeigler).

Be. C.	Beiträge zur klin. Chirurgie.
Be. P. P.	Beiträge zur chem. Physiol. und Pathol. (Hofmeister).
Bel. m.	Belge médical.
Bi. C.	Biochemisches Centralblatt.
Bib. M.	Bibliotheca medica.
Bio. C.	Biophysikalisches Centralblatt.
Bo. G.	Bollettino della r. Accad. med. di Genova.
Br. M.-C. J.	Bristol Medico-Chirurgical Journal.
Brain.	Brain.
Bu. g. t.	Bulletin général de Thérapeutique.
Bu. H.	Bulletins et Mémoires de la Soc. méd. d. Hôp. de Paris.
Bu. J. H. H.	Bulletin of Johns Hopkins Hospital.
Bu. L.	Bullettino della Soc. Lancisiana degli Ospedali di Roma.
Bu. M.	Bulletin médical, Le.
Bu. P.	Bulletin de l'Acad. de Médecine (Paris).
Bu. R.	Bullettino della Reale Accademia med. di Roma.
C. a. P.	Centralblatt für allgemeine Pathologie.
C. B.	Chemisches Berichte.
C. C.	Centralblatt für Chirurgie.
C. G.	Centralblatt für Gynäkologie.
C. H.	Centralblatt für Haut- und Geschlechtskr.
C. i. M.	Centralblatt für innere Medicin.
C. J.	Clinical Journal.
C. J. M.	Cleveland Journal of Medicine.
C. K.	Centralblatt für die Krankh. d. Harn- und Sex. Org.
C. k. m.	Centralblatt für klinische Medicin.
C. M.	Centralblatt für d. gesammte Medicin.
C. M. i.	Clinica medica italiana.
C. M. Pa.	Clinica medica gener. di Parma.
C. m. W.	Centralblatt für die medicinischen Wissenschaft.
C. N.	Centralblatt für Neurologie.
C. P.	Centralblatt für Physiologie.
C. r. A. M.	Compte-rendu de l'Acad. de Médecine.
C. r. A. S.	Comptes rendus de l'Académie des Sciences.
C. r. S. B.	Comptes rendus des Séances et Mém. de la Soc. de Biologie.
C. S.	Centralblatt für Stoffwechsel und Verdauungs-krankh.
C. s. A.	Correspondenz-Blatt für schweizer Aerzte.
C. St.	Clinical Studies (Bramwell).
C. Z.	Chemisches Zeitung.
Ch. An.	Charité Annalen.
Cl. M.	Clinica moderna, La.
Co. M.	Congrès français de Médecine.
Ct.B.	Centralblatt für Bakteriologie.
Ct. P. S.	Centralblatt für d. ges. Phys. u. Path. des Stoffwechsel.
Ct. T.	Centralblatt für gesammte Therapie.
D. A.	Dubois Archiv.
D. Ar. M.	Deutsches Archiv für klin. medicin.
D. J. M. S.	Dublin Journal of Medical Science.
D. K.	Deutsche Klinik.
D. m. W.	Deutsche medicinische Wochenschrift.
D. M.-Z.	Deutsche Medizinal-Zeitung.

D. Z.	Deutsche Aerzte-Zeitung.
D. Z. C.	Deutsche Ztschr. für Chirurgie.
D. Zt.	Dermatologisches Zeitschrift.
E. A.	Experimental Archiv.
E. H. R.	Edinburgh Hospital Reports.
E. M. J.	Edinburgh Medical Journal.
Eng. A.	Engelmann's Archiv.
Er. P.	Ergebnisse der Pathologie (Lubarsch u. Ostertag).
Er. Ph.	Ergebnisse der Physiologie (Ascher u. Spiro).
F. B.	Festschrift für Bischoff.
F. h.	Folia hæmatologia.
F. L.	Finska Läkarssällskapet's Handlingar.
F. M.	Fortschritte der Medicin.
F. P.	Florence Labor. de Physiol. Résumé des Travaux.
G. m. B.	Greifswalder medicinische Beiträge.
G. M. C.	Mitteil. a. d. Grenzgebieten der Med. und Chir.
G. M. J.	Glasgow Medical Journal.
G. m. P.	Gazette médicale de Paris.
G. O.	Gazzetta degli Ospedali.
G. O. C.	Gazzetta Ospedali e Clin.
G. T.	Gazzetta medica di Torino.
Ga. H.	Gazette des Hôpitaux.
Gi. i. S.	Giornale internaz. d. Scienze med.
Gi. M. v.	Giornale ital. della Mal. ven. e della pelle.
Gi. T.	Giornale d. reale Accademia di Med. du Torino.
Gu. H.	Guy's Hospital Reports.
Gz. H.	Gazette hebdomadaire.
H.	Hospital.
H. C.	Hygienisches Centralblatt.
H. R.	Hygienisches Rundschau.
H. S. / Hos.	Hospitalstidende.
I. D. C.	International Dermatological Congress.
I. M. C.	International Medical Congress.
I. R.	Internationale klinische Rundschau.
I. T. C.	International Tuberculosis Congress.
In. C.	International Clinics.
In. C. L.	Internat. Centralb. f. Laryngologie.
J. A. M. A.	Journal of the American Medical Association.
J. A. P.	Journal de l'Anatomie et de la Physiologie.
J. A. & P.	Journal of Anatomy and Physiology.
J. B. C.	Journal of Biological Chemistry.
J. B. & C.	Journal of Balneology and Climatology.
J. C.	Journal of the American Chemical Society.
J. C. D.	Journal of Cutaneous and Gen.-Urin. Diseases.
J. D. S.	Journal de Dermat. et de Syphil.
J. E. M.	Journal of Experimental Medicine.
J. H. H. R.	Johns Hopkins Hospital Reports.

J. Hy.	Journal of Hygiene.
J. La.	Journal of Laryngology, Rhinology, and Otology.
J. M.	Journal des Maladies Cutan. et Syph.
J. M. B.	Journal de Médecine de Bordeaux.
J. M. R.	Journal of Medical Research.
J. M. Sc.	Journal of Mental Science.
J. mil.	Journal de Médecine militaire.
J. N. & M.	Journal of Nervous and Mental Disease.
J. O. & G.	Journal of Obstetrics and Gynæcology of the British Empire.
J. P.	Journal of Physiology.
J. P. & B.	Journal of Pathology and Bacteriology.
J. P. C.	Journal für prakt. Chemie.
J. P. P. G.	Journal de Physiologie et de Pathologie générale.
Ja. G.	Jahrbücher über Gynäkol. und Geburtsch.
Ja. H.	Jahrbücher d. Hamburgischen Staatskrank.
Ja. K.	Jahrbücher für Kinderheilkunde.
Ja. M.	Jahrbücher der in- und auslandischen gesammte Med. (Schmidt).
Jan.	Janus.
Jb. L. M.	Jahresbericht ü. d. Leistungen u. Fortschr. in d. ges. Med.
Jb. L. O.	Jahresber. u. d. Leist. u. Fortschr. in Gebiete der Ophth.
Jb. T.-C.	Jahresber. u. d. Fortschr. der Thier-Chemie.
Jo. B.	Journal de Médecine (Bruxelles).
Jo. P.	Journal de Pharmacie et de Chimie.
K. i. M.	Kongress für innere Medicin.
K. J.	Klinisches Jahrbüch.
K. S.	Korrespondenz-Blatt für Schweizer Aerzte.
K. T. W.	Klinische-Therapeutische Wochenschrift.
K. V.	Korrespondenz-Blätter d. allg. ärztl. Vereins von Thüringen.
K. W.	Korrespondenzbl. d. Württemb. ärztl. Landesv.
L.	Lancet.
L. m.	Lyon médical.
La. R.	Laboratory Reports, Roy. Coll. Phys., Edinburgh
Li. M.-C. J.	Liverpool Medico-Chirurgical Journal.
M.	Morgagni, Il.
M. A. B.	Mémoires de l'Acad. roy. de Belgique.
M.-C. T.	Medico-Chirurgical Transactions.
M.-C. U.	Medicin.-Chemische Untersuchungen.
M. Chr.	Medical Chronicle.
M. H.	Middlesex Hospital.
M. i.	Médecine infant., La.
M. K.	Medicinische Klinik.
M. M.	Medical Magazine.
M. m.	Médecine moderne, La.
M. M. J.	Montreal Medical Journal.
M. N.	Medical News.
M. N. A.	Memoirs of the National Academy of Sciences.
M. O. A.	Magyar Orvosi Archivum.
M. R.	Medical Record.
M. Rev.	Medical Review.
M. T.	Medical Times and Gazette.
Ma.	Maly's Jahrbuch.

Mit. B.	Mitteilungen aus der Berlin phys. Gesell.
Mit. H.	Mitteilungen aus der Hamburg. Staatskrankenanstalten.
Mit. K.	Mitteilungen aus der med. Klinik zu Königsberg.
Mit. U.	Mitteilungen der Kgl. Ges. d. Wiss. zu Upsala.
Mit. W.	Mitteilungen aus der med. Klinik zu Würzburg.
Mo. C.	Monatsschrift für Chemie.
Mo. D.	Monatshefte für praktische Dermatologie.
Mo. G. G.	Monatsschrift für Geburtsch. und Gynäkologie.
Mo. K.	Monatsschrift für Kinderheilkunde.
Mo. m.	Montpelier médical.
Mo. U.	Moleschotts Untersuch. zur Naturlehre.
Mü. m. W. Mu. m. W.	Münchener med. Wochenschr.
N. A. S.	Memoirs of the National Academy of Sciences.
N. B.	von Noorden's Beiträge.
N. C.	Neurologisches Centralblatt.
N. C. T.	Nuova clin. terap., La.
N. I. S.	Nouvelle Iconographie de la Salpêtrière.
N. k. A.	von Noorden's klinische Abhandlung.
N. m. A.	Nordiskt medicinskt Arkiv.
N. T.	Nederlandsch Tijdschrift voor Geneeskunde
N. V.	Naturw. Verein. f. Neuvorpommern.
N. Y. J.	New York Medical Journal.
N. Y. M.	New Yorker medicinische Monatssch.
N. Y. & P. J.	New York and Philadelphia Medical Journal.
P.	Policlinico, Il.
P. L.	Przeglad Lekarski.
P. m.	Presse médicale, La.
P. m. b.	Presse médicale belge, La.
P. M. J.	Philadelphia Medical Journal.
P. P. C.	Proceedings of the Philadelphia County Medical Society
P. R.	Proceedings of the Royal Society (London).
P. R. Ed.	Proceedings of the Royal Society of Edinburgh.
P. T.	Philosophical Transactions of the Royal Society.
P. V.	Prager Vierteljahrsschr.
P. W.	Prager medizinische Wochenschrift.
Pa. M. T.	Philadelphia Medical Times.
Ped.	Pediatria, La.
Pr.	Practitioner.
Pro. M.	Progressive Medicine.
Pro. mé.	Progrès médical, Le.
R. c.	Revista clinica.
R. c. c.	Rivista critica clinica.
R. c. M.	Rivista gén. ital. di clin. med.
R. c. P.	Rivista di clin. Pediatr.
R. c. t.	Revue générale de clinique et thérapeutique
R. M.	Riforma medica.
R. M. E.	Revue mensuelle des Mal. des Enfance.
R. m. M. C.	Revue mensuelle de Méd. et Chir.
R. m. R.	Russische medicin. Rundschau.
R. N. P.	Review of Neurology and Psychiatry.

R. P.	Russische Arch. der Pathologie.
R. T.	Revue de Thérapeutique.
R. v.	Rivista veneta di Scienze mediche.
R. Z. D.	Russische Ztschr. f. Dermat.
Re. C.	Revue de Chirurgie.
Re. Gy.	Revue de Gynécologie et Chir. abdom.
Re. M. Re. m.	Revue de Médecine.
Ri. c.	Rivista clinica e terapeutica.
Riv. M.	Rivista di medicina.
S.	Sperimentale, Lo.
S. B.	Société de Biologie.
S. b. A.	Sitzungsber. d. königlich-bayer. Akad. d. Wiss. zu Münch.
S. E.	Sitzungsber. der physikal.-med. Soc. zu Erlangen.
S. J.	Scottish Medical and Surgical Journal.
S. K.	Sitzungsber. d. Kaiserl. Akad. d. Wissen. (Math.-natur. Kl.).
S. M.	Sitzungsber. d. Gesell. f. Morphol. u. Physiol. zu München
S. m. A.	Sammlung med. Abhandlung.
S. m. H.	Société méd. d. Hôpitaux.
S. n. G.	Sitzungsber. d. niederrh. Gesell. f. Natur.- und Heilkunde.
S. W.	Sitzungsber. d. phys.-med. Gesell. zu Würzburg.
S. W. A.	Sitzungsber. d. Kaiserl. Akad. d. Wissen. (Math.-natur. Kl.).
S. W. D.	Sitzungsber. d. Wien dermat. Gesell.
Sc. W.	Schweiz Wchnschr. f. Chem. u. Pharm.
Se. M.	Semaine médicale.
Set. M.	Settimana medica, La.
Sit. M.	Sitzungsber. d. Gesell. z. Beforderung d. Ges. Nat. z. Marburg.
Sk. Ar. P.	Skandinavisches Archiv für Physiologie.
St. B. H.	St. Bartholomew's Hospital.
St. B. J.	St. Bartholomew's Hospital Journal.
St. P.	St. Petersburger medicin. Wochenschr.
St. T. H.	St. Thomas's Hospital.
T. A. A. P.	Transactions of the Association of American Physicians.
T. A. S. A.	Transactions of the American Surgical Association.
T. C. P. P.	Transactions of the College of Physicians of Philadelphia.
T. Cl. S.	Transactions of the Clinical Society of London.
T. Co. A. P.	Transactions of the Congress of American Physicians and Surgeons.
T. F.	Travaux du Laboratoire de L. Frédéricq.
T. G.	Therapie de Gegenwart.
T. M.	Therapeutische Monatsshefte.
T. M. S.	Transactions of the Medical Society of London.
T. O. S.	Transactions of the Obstetrical Society of London.
T. P. S.	Transactions of the Pathological Society of London.
Th. G.	Therapeutic Gazette.
U. A. M.	Ungarisches Archiv für Medizin.
U. m.	Union médical, L'.
U. M. M.	University Medical Magazine.
U. P.	Ungarische Medizin.-chir. Presse.
U. Pa.	University of Penna. Med. Bulletin.
U. S. D. B.	United States Department of Agriculture Bulletin.

V. b. A.	Verhandl. d. böhmischen Akad. der Wissensch.
V. B. M.	Verhandl. d. Berliner medicin. Gesell.
V. C. M.	Verhandl. d. Congresses f. inn. Med.
V. d. G.	Verdandl. d. deutschen pathol. Gesell.
V. f. A.	Verhandl. d. finnischen Aerzte.
V. G. K.	Verhandl. d. Gesell. f. Kinderh.
V. i. M.	Verein für innere medicin zu Berlin.
V. K. D.	Verhandl. d. Kongr. d. d. Dermat. Gesell.
V. n. A.	Verhandl. d. d. naturfors. u. Aerzte.
V. n. G.	Verhandl. d. naturforsch. Gesell. in Basel.
V. n. V.	Verhandl. d. Naturf.-Versamm. in Meran.
V. p. G.	Verhandl. d. physiol. Gesell. in Berlin.
V. s. G.	Verhandl. d. Schles. Gesell. f. vaterl. Kultur.
V. W. G.	Verhandl. d. phys.-med. Gesell. in Würzburg.
Vo. s. V.	Volkmann's Sammlung klin. Vorträge.
W.	Wratsch.
W. A.	Wiener Akademie.
W. Ab.	Würzburger Abhandl. a. d. Gesam. der prak. Heilk.
W. J.	Wiener medicinische Jahrbücher.
W. K.	Wiener Klinik: Vortr. a. d. gesamm. prak. Heilk.
W. k. R.	Wiener klinische Rundschau.
W. k. W.	Wiener klinische Wochenschrift.
W. L. J.	West London Medical Journal.
W. m. B.	Wiener medicinische Blätter.
W. m. P.	Wiener medicinische Presse.
W. m. W.	Wiener medicinische Wochenschrift.
W. V.	Würzburger Verhandlungen.
W. Z.	Wiener Zeitschrift.
Y. J.	Yates and Johnson Laboratory Reports.
Z. a. C.	Zeitschrift für anal. Chemie.
Z. a. P.	Zeitschr. f. allg. Physiologie.
Z. B.	Zeitschr. f. Biologie.
Z. C.	Zeitschr. f. angewandte Chemie.
Z. d. p. T.	Zeitschr. f. diätet. und physikal. Therapie.
Z. e. P.	Zeitschr. f. exper. Pathologie.
Z. G. G.	Zeitschr. f. Geburtsch. u. Gynäkol.
Z. H.	Zeitschr. f. Heilkunde.
Z. Hy.	Zeitschr. f. Hygiene.
Z. M.	Zeitschr. f. klin. Medicin.
Z. N.	Zeitschr. f. Nervenheilkunde.
Z. P.	Zeitschr. f. Psychologie.
Z. P. A.	Zeitschr. f. allg. Pathol. und path. Anat.
Z. p. A.	Zeitschr. f. prakt. Aerzte.
Z. P. C. Z. p. c.	Zeitschr. f. physiol. Chemie.
Z. r. M.	Zeitschr. f. rationelle Medizin.
Z. T.	Zeitschr. f. Tuberkulose.
Z. V.	Zeitschr. f. Vatermarkande.
Ze. P. P. S.	Zentralbl. f. d. gesamm. Physiol. und Path. d. Stoffwech.

THE PATHOLOGY OF METABOLISM

CHAPTER I

DIABETES MELLITUS

By CARL von NOORDEN.

Translated by Herbert French, M.D., M.R.C.P.

So long as we know no more about the nature of the diabetic process than we do at present we must, in common with former generations, define diabetes mellitus in terms of its most important clinical symptom—as a chronic disease in which grape-sugar is excreted in the urine.

This definition, however, needs certain limitations, of which the following may be mentioned :

1. The quantity of sugar must be demonstrable by the ordinary clinical tests. The question whether normal urine contains traces of grape-sugar, to be detected only by the most delicate methods, may be left for the moment.

2. The grape-sugar must occur in the urine when the carbohydrate in the food is not more than that in ordinary human diet, or when the carbohydrate food is reduced in quantity or even stopped altogether. Cases where glycosuria only occurs after partaking of unusually large quantities of carbohydrate can scarcely be regarded as diabetes mellitus in a clinical sense.

3. The tendency to glycosuria must be persistent—that is to say, it must last at least some weeks or months. There are many conditions of ill-health in which a temporary disposition to glycosuria occurs. Such are not called diabetes mellitus, although there is considerable evidence that in both cases the glycosuria has the same fundamental cause (see Anomalies of Pancreatic Function).

In order not to load this chapter with questions which have only a slight, and perhaps even only an apparent, connection with true diabetes mellitus, certain forms of carbohydrate excretion, such as pentosuria, the pure form of lævulosuria, and phloridzin diabetes, are considered in a separate chapter.

I.—THE PATHOGENESIS OF GLYCOSURIA.

Physiology teaches us that the normal quantity of sugar in human blood is about 1 part per thousand. According to twenty recent observations made in my wards by Stern and Liefmann, the minimum = 0·65, the maximum = 1·05, the average = 0·85. These were the quantities actually present as grape-sugar, the results being similar to the previous observations of Pickardt, Miura, and Hanriot (1). Whether or not the sugar in the blood demonstrable by analysis exists as free glucose, or partly or wholly in loose combination with other molecules—for example, as jecorin or as colloid sugar—is a question which is discussed in Vol. I. In passing, it may be mentioned that it seems more than probable that Fischer's isomaltose is present in the blood [F. W. Pavy and R. L. Slau (2)]. It is not known to have any relationship with diabetes.

Some experiments of Embden's, in which he perfused blood through the liver, suggest that the blood contains some antecedent of sugar whose nature is not yet established (2A).

The kidneys are impervious to the quantities of sugar mentioned above. Glycosuria occurs :

1. When the kidneys from any cause become less impervious to sugar. This is typically the case in phloridzin-poisoning (compare the chapter on Toxicology of Metabolism). It is uncertain whether or not circumstances may arise in human pathology in which the kidneys become abnormally pervious to sugar, a condition which one might term " renal diabetes mellitus."

2. When the blood from any cause becomes abnormally rich in sugar (hyperglycæmia). It has been generally assumed since the time of Claude Bernard's classical researches that hyperglycæmia is the immediate cause of diabetic glycosuria.

3. When the sugar in the blood is less firmly combined than usual. This is a newer theory of the origin of diabetic glycosuria. It is based on the discovery that in the organs [Drechsel (3)] and in the blood [Baldi, Jacobsen, Bing, von Henriques (4)] part of the sugar is combined with lecithin in the form of jecorin. Kolisch (5) has propounded the view that the kidneys may be impervious to jecorin, but not to free glucose. The normal blood sugar may be jecorin. It is possible that in diabetes the power to form jecorin is defective, so that abnormal quantities of free glucose are present in the blood, and thence are excreted by the kidneys. If this be so, it is not simple hyperglycæmia which is the cause of glycosuria, but a pathological change in the constitution of the sugar in the blood. This hypothesis, however, is now discarded, partly through the work of Bing (4), partly because some new researches of Kolisch and von Stejskal's (6) have shown that Kolisch's former methods were unreliable.

Although upon various grounds it seems likely that the sugar does not circulate free in the blood, but perhaps in colloid combination and form, yet our present knowledge upon this point affords no firm basis

upon which to found a theory of diabetes. Indeed, it is not definitely established that there is any difference between the healthy and the diabetic blood sugar. This aspect of the question will not be further discussed here.

A.—GLYCOSURIA DUE TO UNDUE PERMEABILITY OF THE KIDNEYS TO SUGAR—RENAL DIABETES.

It has been mentioned that phloridzin-poisoning leads to a true renal diabetes. This important discovery of von Mering's (7) will not be more fully discussed just now. It is known that, though diseased kidneys with degenerate epithelium might well be expected to let sugar through more easily than do healthy kidneys, the facts show this not to be so. Rather is the reverse the case, to judge from clinical experience. Diabetics often pass less sugar, or even become cured of their glycosuric tendency, if chronic Bright's disease develops as a complication (8). This fact has been long familiar to physicians, and has recently become more and more established. I could quote several examples from my own practice. We are ignorant of the reason why, but it seems certain that in some severe forms of nephritis the kidneys exhibit a diminished permeability to sugar. There is then very little sugar in the urine and much sugar in the blood. Achard has published one clinical observation of this kind (9). Perhaps a case of Lépine's (10) should be put into this category. In my wards recently there was a patient suffering from slight diabetes and advanced Bright's disease. Typical uræmia set in. The blood contained the enormous amount of 0·85 per cent. of sugar; the urine at the same time contained only 1·4 per cent. Such figures are an obvious and remarkable departure from the usual condition of affairs.

Probably the sudden drop in the sugar in the urine in the final coma and death agony is at least partly to be explained by deficient kidney activity. In one such case—and without nephritis, be it noted—we found 1·01 per cent. of sugar in the blood, and in the urine only traces. It is true that in many of these cases the diminished intake of food accounts for the drop. Clinical observations are supported by experimental work. In dogs from whom the pancreas has been ablated, and in whom kidney complications have been produced by chromic acid poisoning, Schupfer (11) has demonstrated a diminished glycosuria; whilst Richter, Ellinger, and Seelig (12) showed there was a simultaneous rise in the sugar in the blood. Stagnation of blood sugar, the result of kidney insufficiency, can only explain the phenomena when they are transient, as in the death agony. For the explanation of the lasting decrease of glycosuria after the onset of chronic nephritis other causes must be sought for. At the moment, however, there are practically no data available for discussion. The conditions just described are the exact converse of that which we have termed "renal diabetes," the fundamental cause of which, as we have said, would be an abnormally free permeability of the kidneys for sugar.

On the other hand, Jacobi points out that caffeine, which stimulates the renal epithelium, favours the occurrence of alimentary glycosuria in rabbits (13). He suggests that here both the increased outflow of urine and the glycosuria depend upon a renal factor. Neumann believes he has met with the same phenomena in man (14). In a patient suffering from heart disease diuretin not only produced a greatly increased urine excretion, but also a temporary glycosuria, which was not otherwise present in this patient.

Schupfer maintains a similar view, but found glycosuria only resulted when quite considerable quantities of sugar were given in the food at the same time (11). Strauss carried out the same clinical experiment, and found the result negative (15). I have again and again given large quantities of sugar and other carbohydrates to patients with cardiac and renal disease at the height of diuretin diuresis, and never once have I met with the results mentioned by Neumann. The test must be followed by positive results in a large number of cases before it will be safe to refer the resulting glycosuria to a renal origin. Richter, in a very careful piece of work, has shown that in the diuretin glycosuria there is an increased percentage of sugar in the blood. He compares the condition to the ordinary form of " hepatogenous glycosuria " (16). Rose and Schilling (17) confirm this statement.

We must not forget an observation of Richter's and Kossa's upon animals (17). They found that extremely slight affections of the kidney, such as result from minute doses of cantharides and chromic acid, seem to favour the onset of glycosuria, whereas severe nephritis is unaccompanied by sugar in the urine. In Richter's experiments, however, the glycosuria cannot have been purely renal, because there was a distinct though slight rise in the sugar in the blood at the same time. The question arises whether the cantharides may not have an important action upon the pancreas in addition to that which it exerts upon the kidneys. Kóssa found no hyperglycæmia, but the glycosuria was so slight that the necessary increase in the sugar of the blood was perhaps so little as to fall within the limits of error of the analyses.

Turning now to the clinical aspect of diabetes, there are extremely few observations capable of assisting us to answer the question one way or the other. For the diagnosis of a renal diabetes it would be necessary[1]—

1. That the glycosuria should be within wide limits independent of the amount of carbohydrate taken in the food.

2. That the sugar in the blood should at least not be increased, but should rather be diminished, as it is in phloridzin diabetes, in consequence of the drainage of sugar from the kidneys.

[1] Some authorities, particularly Naunyn (18), insist, further, that there must be a definite time-relation between the onset of the kidney disease and of the glycosuria. Naunyn is inclined to speak of renal diabetes even when a veritable Bright's disease without doubt preceded the diabetes. If this be granted, it would place the conception of " renal diabetes " upon quite a different basis to that in our text. It would no longer be a question of whether or not there is a form of diabetes in which the kidneys excrete sugar with the urine from increased permeability, the sugar in the blood being normal or less than normal. From Naunyn's observations we will only borrow this interesting and important clinical fact: that granular kidney patients relatively seldom suffer from diabetes, whereas the reverse relationship is much more common.

Of these two points, I consider the former to be the less important. The same phenomena occur in the most manifold forms and degrees even in ordinary diabetes mellitus. I will only mention here my experience with the "oats cure" of diabetics. Patients who passed much sugar in their urines even on the most rigid diabetic diet within a short while were passing no sugar at all when they took large quantities of oats—up to 250 grammes and more daily. In early cases of diabetes the rule seems to me to be that the glycosuria varies widely and quite independently of any progressive increase in the carbohydrate diet. In some disorders of the circulation, in acromegaly, and in cases of cerebral tumour accompanied by glycosuria, I have for a long time noticed the same thing, until later an ordinary severe diabetes developed, and the amount of glycosuria became much more closely related to the amount of sugar in the food.

The second point is certainly the more important, provided the conditions included in the first are at the same time fulfilled.

Klemperer has described one case which has been often quoted, but which is very difficult to understand. The sugar in the urine was 0·35 per cent., that in the blood 0·18 per cent. (19). We cannot agree with Naunyn in regarding this proportion of sugar in the blood as small. Lüthje once found sugar in the blood 0·05 per cent., in the urine 0·65 per cent.; so small a proportion of sugar in the blood is very improbable. Lüthje himself now doubts that his case can be accepted as a proof of the existence of a "renal diabetes." Kolisch and Buber (19) once found 5 per cent. of sugar in the urine, with 0·14 per cent. in the blood, a difference which, after more recent observations, does not appear so remarkable as it did formerly (19) (*vide infra*).

The material to hand, to which perhaps may be added one or two observations made by myself, is very scanty. The conclusions permitted by even these few cases are rendered very indefinite by the well-known difficulty of estimating sugar in the blood with anything like accuracy. Too much is seldom, too little very often, found, even by the most careful workers, on account of the sources of analytic error. A broader basis of comparative analyses of sugar in the urine in the blood is urgently needed before one can base upon them the existence of a renal diabetes. The matter is of great importance, and fundamental in the study of diabetes. Further, there must be proof from the wards that the cases diagnosed as "renal diabetes" exhibit permanent differences from ordinary cases of diabetes mellitus, and not only during a few weeks or months. It would then be a question of an entirely different disease, agreeing with true diabetes mellitus only in the glycosuria and in the phenomena directly dependent upon this. *A priori*, the existence of renal diabetes would be expected, for the possibility that the kidneys may become pervious to sugar under the influence of spontaneous disease or of certain endogenous or exogenous poisons has been clearly established since the discovery of phloridzin diabetes. Nevertheless, the foundations of the clinical symptomatology of "renal diabetes" are still to be laid. It is as yet but a castle in the air.

The question whether or not there is any " renal element " in diabetic glycosuria was first raised by Lépine (20), and again brought up by Klemperer. In the light of present-day knowledge it may be answered as follows :

1. There are certainly kidney disorders which hinder the passage of sugar into the urine.

2. There is an experimental form of diabetes dependent upon abnormal permeability of the kidneys. Phloridzin diabetes is of this nature, and possibly other toxic glycosurias also (caffeine ?).

3. The existence of a renal diabetes as an independent disease has not yet been proved (21).

B.—GLYCOSURIA DUE TO HYPERGLYCÆMIA.

It has been generally held since Claude Bernard's classical researches that hyperglycæmia is the actual cause of the escape of sugar through the kidneys in diabetes (22). The kidneys are only impervious to a certain percentage of sugar in the blood. What are the limits ? Claude Bernard used inexact methods, but estimated the percentage in normal blood approximately, regarding 0·2 to 0·3, and even 0·4 per cent. as healthy. According to later researches by Pavy, Seegen, and particularly Naunyn, and others (23), we must regard anything in excess of 0·15 per cent. as hyperglycæmia. Probably the normal limit is even lower in man. Naunyn puts the reducing power of normal human blood at 0·08 to 0·09 per cent. of grape-sugar. The observations made in my own laboratory gave figures even lower than this, and 0·1 per cent. of grape-sugar probably constitutes hyperglycæmia. In diabetic men the values found have been almost without exception higher. Frerichs, Pavy, Seegen, and Naunyn frequently found 0·3 to 0·4 per cent. (24). The highest figures recorded are those of Naunyn (0·7 per cent.) and Lépine (20) (1·06 per cent.). I have mentioned two analyses in which 0·85 per cent. and 1·01 per cent. were present. In dogs, after extirpation of the pancreas, the sugar in the blood is considerably increased in a similar way. This was first shown by the observations of von Mering and Minkowski in pancreatic diabetes (25), and has been thoroughly confirmed, notably by Lépine (26).

Some authors—for example, Pavy—believe there is a regular relationship between the sugar of the urine and that of the blood ; others—for instance, Frerichs and Naunyn—could find no such arithmetic proportions. The following is Pavy's (23) table :

Sugar in 1,000 *Parts of Blood.*	*Sugar in* 1,000 *Parts of Urine.*
5·76	109·9
5·54	94·1
4·97	93·4
2·79	45·5
2·62	61·3
1·85	48·1
1·54	31·8

In my own wards H. Liefmann and R. Stern found :

Sugar in 1,000 *Parts of Blood.*	*Sugar in* 1,000 *Parts of Urine.*
2·30	>20 (two estimations).
2·41	10–20 (two estimations).
1·74	5–10 (three estimations).
1·55	Traces–5 (six estimations).
1·32	0 (six estimations).

In cases complicated with nephritis without uræmia :

Sugar in 1,000 *Parts of Blood.*	*Sugar in* 1,000 *Parts of Urine.*
3·23	>20 (two estimations).
1·44	0 (three estimations).

The following table shows the quantity of sugar in the blood of patients who had been rendered aglycosuric by strict dieting, or who at most were passing an amount of sugar too small to estimate. The cases are arranged in the order of the duration of their illness, and no nephritis was present :

Duration of the diabetes, >10 years ; sugar in the blood, 0·189 per cent. (two estimations).
Duration of the diabetes, 4 to 5 years ; sugar in the blood, 0·175 per cent. (two estimations).
Duration of the diabetes, 1 to 3 years ; sugar in the blood, 0·143 per cent. (two estimations).
Duration of the diabetes, <1 year ; sugar in the blood, 0·109 per cent. (five estimations).

It will be obvious that the results obtained by different observers are not immediately comparable with one another. The quantitative estimation of sugar in the blood is one of the most difficult processes in clinical chemistry. Knapp's method and the gravimetric are alone reliable. There are objections to Pavy's and Seegen's methods of estimation, to say nothing of still older analyses. Great weight, therefore, cannot be attached to Seegen's (28) assertion—that in so-called slight diabetes there is no hyperglycæmia. Probably it was present, but he did not find it. If there had been any talk in his time of "renal diabetes," Seegen must have classed those cases under that heading on account of the relative amounts of sugar in the blood and in the urine ; and yet their whole clinical course characterized them as ordinary diabetes.

The fact is a great many more fundamental observations upon the amounts of sugar occurring in the blood of diabetic patients are needed, and also upon the relation of these amounts to the intensity of the glycosuria. I do not doubt that the doctrine of hyperglycæmia being the immediate cause of diabetic glycosuria will be incontestably established. I should none the less not be surprised if, even in cases of considerable glycosuria, the figures for the sugar in the blood were found scarcely higher than normal ; nor would it astonish me if in some cases the sugar in the blood remained almost constant, whilst that in the urine varied within wide limits. The line at which the kidneys allow sugar to leak through them is probably drawn very finely. If this be so, and the limit be but just overstepped, a very considerable sugar excre-

tion might easily occur without analysis being able to detect any hyperglycæmia [*cf.* Lépine (29)]. I must here mention the excretion of urea. The quantity of urea in the blood is very finely balanced; the slightest excess is immediately eliminated by healthy kidneys; and yet, although the most accurate of the known methods can detect no increase of urea in the blood, the kidneys remove so much that they render the urine a 2 per cent. solution of urea. It is only when the kidneys are overworked or diseased that the reservoir from which the urea is drawn begins to fill up to a higher level. From the comparative analyses of blood and urine carried out in my laboratory, it must be surmised that at the beginning of diabetes glycosuria without apparent hyperglycæmia is the rule. A similar conclusion must be drawn in cases of alimentary glycosuria in which the increase of sugar in the blood is extremely slight, and often is not to be detected at all [Schlesinger (30)]. I am able to compare a clinical observation with Schlesinger's experiments upon animals. One of my assistants had in his blood ordinarily 0·08 per cent. of sugar; after 100 grammes glucose, 0·07 per cent. without glycosuria; after 200 grammes glucose, 0·10 per cent., with glycosuria.

Increased Impermeability of the Kidneys to Sugar.

I should like to commend as a matter for research the question whether or not, in the course of diabetes, the kidney epithelium accommodates itself to the changed conditions, and by a sort of protective process develops an increased impermeability to sugar,[1] even without any complicating nephritis. The consequence would be an accumulation of sugar in the blood, and a persistent hyperglycæmia that could be detected by analysis. Let us think for a moment of the quantitative relationships. If we find 0·2 per cent. of sugar in the blood, that is already a respectable degree of hyperglycæmia; in the total blood in the body there would be some 5 or 6 grammes of sugar over and above the normal. The kidneys, if they were working normally, could easily rid the blood of this in less than one hour. But they do not do so. It is usually assumed that the sugar in the blood remains high because, on the one hand, fresh sugar is constantly being put into the circulation from the sugar sources, and, on the other hand, too little sugar is being burnt up in the tissues. No doubt this is correct. Nevertheless, there should be no such sugar accumulation in the blood if the kidneys were properly performing their function of keeping the blood right. I therefore assume that a certain degree of hyperglycæmia is indeed essential to diabetic glycosuria, but that those high sugar figures which do actually occur, and which are usually in the mind of those who speak of hyperglycæmia, are dependent upon an increased impermeability of the kidneys to sugar. Perhaps, amongst other things, the secretion of the pancreas acts by a sort of "chemical reflex" upon the permeability of the renal filter. In favour of such a view is the rapid appearance of hyperglycæmia after extirpation of the pancreas.

[1] See the previous table.

In diabetes the kidneys maintain their impermeability to sugar in the face of strong diuretics, even against the urine secretion called forth by theobromine and caffeine. In œdematous patients suffering from severe diabetes these drugs often increase the volume of urine only, and do not influence the total quantity of sugar passed. I have several clinical examples of this. These facts are an argument against Jacobi's view of "caffeine glycosuria."

C.—ON THE CAUSES OF HYPERGLYCÆMIA.

If we attribute glycosuria to hyperglycæmia, the next question is, What leads to the overloading of the blood with sugar? I shall not discuss here what substances give rise to the blood sugar. I shall only recall to mind the fact that it may be derived not only from the carbohydrate of the food, but also from proteid molecules certainly, and from fat probably. This must be considered more fully later, in so far as the subject has not already been dealt with in the physiological portion of this work. We are here only concerned with the mechanism of hyperglycæmia.

1. Hepatogenous Hyperglycæmia.

(*a*) *Experimental Work.*

In order to do full justice to clinical observation, it is necessary to cite certain facts that have been learned experimentally. All researches on the matter date from the famous *piqûre* of Claude Bernard. This observer showed that glycosuria lasting several hours resulted in animals when a puncture was made at the apex of the calamus scriptorius in the fourth ventricle. The liver was afterwards found to be free from glycogen.

Glycosuria is absent if the liver be made to contain little or no glycogen before the *piqûre*. This may be accomplished by starvation, deprivation of heat, strychnine-poisoning, febrile disease, ligature of the lymphatic duct, and other means.

The explanation of the experiment can scarcely be contested. It has recently been fully established by Pflüger, who has gone critically through the whole of the experimental data, and drawn the most careful deductions (31). From the stimulated point in the central nervous system centrifugal stimuli pass by the splanchnic nerve to the liver, and these stimuli cause the liver to part with its store of glycogen. According to some, the stimulation acts through the vasomotor nerves; according to others, there is a passage of the nervous stimulus direct to the hepatic cells. It has been suggested that the nerve stimulus may cause an increased formation of diastatic ferment. There have even been surmises that the primary organ affected by the nerves in these experiments is the pancreas. This last is an interesting theory, but it is here beside the mark.

The fact of the sudden discharge of glycogen from the liver is very important. This glycogen leaves the cells as grape-sugar. It causes hyperglycæmia (32), and hence glycosuria. The temporary character of the glycosuria, and its absence in animals poor in glycogen, become clear. Sugar continues in the urine only so long as glycogen is being given up by the liver, at first in quantity, later more sparingly, and only until the excess of sugar due to this glycogen has either been excreted or burnt up or deposited as glycogen again in another place. We regard it as now proven that it is a diastatic ferment in the liver cells which thus converts the glycogen. Perhaps there may be other glycogen depots taking part in the production of hyperglycæmia. Luchsinger has shown that *piqûre* in rabbits causes the muscles to become similarly free of glycogen (33). Pflüger, however, in his masterly critique mentioned above, finds that only the hepatic glycogen has been shown with certainty to be a source of sugar in the urine after *piqûre;* that of the muscles is still open to doubt (31).

Since Claude Bernard performed his experiments, investigation upon this theme has been active. Both in man and animals a large number of lesions have been discovered, each capable of causing temporary glycosuria referable to the disbursement of glycogen. Amongst others are the following : Destruction of the superior and inferior cervical sympathetic ganglia, of the first dorsal ganglion, of the abdominal ganglia, and of other sympathetic nerves ; stimulation of the central end of the cut vagus nerve ; painful stimulation of peripheral nerves ; psychical disturbances ; injury to various parts of the cerebral hemispheres, the midbrain, and cerebellum. It seems possible to elicit experimental glycosuria in animals by almost any severe and sudden paralyzing or exciting lesion to the nervous system. Perhaps the stimulation always passes out from the spot discovered by Claude Bernard in the medulla oblongata. No other lesion is followed by glycosuria with such certainty as is the typical *piqûre* (34).

Besides gross mechanical nerve lesions, certain poisons have the power to produce glycosuria in animals. I may mention CO, CS_2, curare, morphine, strychnine, nitrobenzol, amyl nitrite, uranium salts, salts of mercury, hydrochloric and sulphuric acids, various narcotics and preparations of theobromine and of caffeine. The number grows larger every year.

Whenever transitory glycosuria occurs under these or allied conditions, a rich supply of glycogen in the liver is essential. No sugar is passed by ill-nourished individuals poor in glycogen.[1] The glycosuria usually lasts a matter of hours only ; in but few cases does it continue until the next day.

There can be no doubt that a great number of the above lesions act in fundamentally the same way as does *piqûre*. They cause the glycogen to be expelled from its place of storage, either by means of the nervous system or by direct action on the liver itself. Nevertheless, great caution must be observed before these glycosurias can be termed strictly " hepato-

[1] CO glycosuria [Straub, Rosenstein (52)] and ether glycosuria [Seelig] appear to be exceptions.

genous," like that following *piqûre*. It is at least possible that the actual seat of action, particularly in the case of some of the poisons, may be neither the nervous system nor the liver, but the pancreas.

(*b*) *Clinical Points.*

It is probable that the experiments upon animals mentioned above have their exact counterpart in certain glycosurias in man. There are transitory glycosurias that follow commotio cerebri, brain injury, apoplexy, and those that follow the toxic action of morphia, prussic acid, mineral acids, amyl nitrite, carbon monoxide, phosphorus, chloralamide, chloroform, nitrobenzol, and aniline. Some of these may, indeed, be accounted for by a decreasing power of oxidation in the tissues and consequent defective using-up of sugar. Perhaps this is so in the case of prussic acid, carbon monoxide, and phosphorus-poisoning. There remain, however, a large number of observations, of which the experiments of Bernard and his successors afford the most natural and the clearest explanation. The "clinical" literature is cited under reference (36). It has often been argued that people in whom a temporary glycosuria results from any of the above causes are in a state of latent diabetes; that the particular injury or poison acts only as an exciting factor; and that the latent disease develops fully in due course. This is often the case, no doubt. It only teaches us that a healthy man is little inclined to hepatogenous glycosuria, and that particular conditions must arise to produce phenomena similar to those often observed in animal experiments, especially in rabbits.

I have frequently insisted in my clinical writings that transitory neurogenous and psychogenous glycosuria are almost equivalent terms [von Noorden (37)]. The suspicion at once arises that they are only the first symptoms of a true diabetes that is developing. At the same time there are a few observations which prove with certainty that powerful stimuli may cause transitory glycosuria without any predisposition to diabetes [von Noorden (37A)].

We must remember that transitory glycosurias in man, whether of neuro-traumatic or, still more, of toxic origin, may possibly depend partly upon transient disturbances of the function of the pancreas. It is for the future to determine this. On the other hand, it is justifiable to ask whether many cases of chronic glycosuria, which clinically must be regarded as real diabetes mellitus, may not be entirely neuro-hepatogenous. It may be that a cause, similar to that which experimentally leads to destruction of liver glycogen and hyperglycæmia, is periodically or continuously stimulating Claude Bernard's centre, and thence the liver. An experiment of Eckhard's affords a remarkable analogy. After section of one vagus nerve, stimulation of the central end produced glycosuria. The latter soon disappeared, but, as long as the animal lived, could be again produced at will on stimulating the vagus nerve. Although many physicians are inclined to recognise a true neuro-hepato genous diabetes of this kind, I am not convinced of its existence. With

Pflüger all cases of diabetes should be considered as neurogenous, or else none of them (38A). He who wishes to make a separate pathological entity of neurogenous diabetes must first bring forward evidence that it differs in essential points from ordinary diabetes. Hoffmann tried to do so long ago, but he failed completely, and the attempt is merely of historical interest (39). There are wide variations in the clinical picture presented by diabetes. Slight, progressive, chronic, and acute cases are met with, just as they are in pulmonary tuberculosis ; but these distinctions are quantitative rather than qualitative. The course of the disease is modified by peculiarities in the general constitution, by complications that may arise, and not to any marked degree by any nervous factor. This is more clearly seen at the beginning of the affection, and in the milder cases, than it is in the later stages or in the severe types. All this, however, is not enough to prove, or even to allow one to suspect, that the different clinical pictures represent different diseases.[1]

My opinion is that one must recognise in human pathology neuro-hepatogenous acute glycosurias, both in diabetics and in non-diabetics ; but that in regard to the doctrine of neuro-hepatogenous chronic diabetes mellitus there is ground for the greatest scepticism.

2. Pathological Alimentary Glycosuria.

The term "alimentary glycosuria" is used to denote the excretion of sugar brought about by excessive carbohydrate diet in non-diabetic persons. The question of where the limit lies beyond which an increase of carbohydrate diet leads to glycosuria even in the healthy has been discussed in the physiological portion of this work. Concerning the amount of sugar in the blood in cases of physiological alimentary glycosuria, *vide* Index.

It is the pathological exacerbation of this phenomenon which concerns us here. In testing for pathological alimentary glycosuria, it is usual to give in one dose either 100 grammes of cane-sugar or grape-sugar, or under certain circumstances glucose, either in the early morning on an empty

[1] Many physicians are extremely ready with the diagnosis, "neurogenous diabetes." This arises partly from their desire to calm their patients by calling their complaint "nervous," in distinction to "constitutional" ; partly because they allow themselves to be deceived by certain phenomena which may be observed in almost all cases of diabetes which are watched with sufficient care over a considerable time. In the early stages of diabetes—I might almost say so long as it is hardly more than a condition of slight glycosuria in the sense of Seegen and Traube—the sugar in the urine is influenced, not only by diet, but also by elevation and depression of spirits, efforts of mind and body, injuries, and illnesses of various sorts. This is particularly the case in neurasthenics. Measures which lead to a general increase in strength and improvement of the neurasthenia almost always bring about diminished glycosuria at the same time. When such a case is seen, there is an inclination to diagnose "neurogenous diabetes," whereas one really has to do with an ordinary diabetes, to whose alimentary factors a neurogenous, or, perhaps better, a neuro-hepatogenous glycosuria has been added.

In the study of diabetes in later stages these variations in the glycosuria are exhibited far less often, or, at least, they are far less easy to demonstrate. The dependence of the glycosuria upon diet is then the prominent point in the clinical picture [von Noorden (37)]. The nervous factors are far in the background.

How often have I seen cases at first diagnosed as obvious "nervous diabetes" pass on, in the course of a year or two, into the most severe forms of the disease!

stomach or two hours after a small breakfast. The urine of healthy persons should remain free from sugar. If glycosuria results, it is usually attributed to "inefficiency of the liver."[1] Hofmeister (40) describes it as a "decreased limit of assimilation." It is assumed that the liver is unable to deal with the increased amount of sugar inundating it from the portal vein—that is to say, it cannot polymerize it, and fix it completely as glycogen. This explanation can hardly be controverted. The question is, What does the inefficiency of the liver depend upon? The cause cannot be overfilling of the glycogen reservoir, by which we explain the alimentary glycosuria of healthy persons. In most cases the sufferers are out of health, and their previous diet the reverse of excessive, so that there is no reason to suppose that their glycogen depot was already brimful. There is no more reason for supposing that they have less power of making use of sugar. In none of the affections in question are the processes of oxidation and of energy production decreased; rather is there a great increase in oxidation, and particularly in the combustion of carbohydrate in several of the diseases, such as Graves' disease and high fever, which predispose to alimentary glycosuria.

Either the liver cells are unable to polymerize all the sugar reaching them, or else the glycogen formed becomes saccharified too quickly, through some increase in the diastatic process. The latter would imply that the automatic regulation between sugar combustion and sugar formation is no longer so evenly balanced as in health. Physiologically, the diastatic process is dependent only on the sugar requirements of the body; here it would also be controlled by the sugar-supply.

So far the theory of pathological alimentary glycosuria is not so very difficult to follow. As soon, however, as we begin to inquire, further, what conditions cause derangement of the storage of glycogen and of its reconversion by diastatic influence, the ground becomes much less secure.

For a long while endeavours were made to find the cause in a pathological change in the liver cells themselves—*insuffisance hépatique* in the closest sense of the term. This idea was completely negatived when attempts were made to produce alimentary glycosuria in patients with diseased livers by giving them grape- or cane-sugar. There is only one form of alimentary sugar excretion for which the liver cells themselves are with any certainty responsible, and that is alimentary lævulosuria. I myself am unable from my own researches to allow that it is so constant an accompaniment of diseases of the liver parenchyma as many authors assert, but it is, nevertheless, very striking:

[1] Many observers, when they wish proof of pathological alimentary glycosuria, particularly that of *insuffisance hépatique*, give cane-sugar instead of grape-sugar. This is wrong. The conditions are not the same in the case of these two different sugars. Of the cane-sugar, the whole of that which is not broken up into monosaccharide in the intestine, but reaches the blood unaltered, is excreted in the urine. Neither the liver nor any other organ has the power to split up and assimilate cane-sugar. Its occurrence in the urine, therefore, is no proof of overloading of the liver with glycogen, or of *insuffisance hépatique*, but shows that the ferment in the succus entericus which splits up cane-sugar has not been fulfilling its functions. The liver is only concerned in the mellituria when, besides the cane-sugar, glucose appears in the urine. To determine this quantitatively is too complicated to allow of the cane-sugar test being recommended for clinical purposes.

1. How frequently and how markedly it may occur in cases of liver disease.

2. That it is very often found in these patients, even when the tests with dextrose and saccharose are negative.

3. That in no other affection—not even in diabetes mellitus—does the excretion of sugar after giving lævulose (lævulosuria) exceed that from giving grape-sugar and cane-sugar so much as it does in liver diseases.

Alimentary lævulosuria is also often found in diseases with high fever—particularly pneumonia—and in advanced failure of cardiac compensation. These exceptions prove the rule; for in these very diseases pathological changes in the liver are extremely common—for example, cloudy swelling and cyanotic induration. On the other hand, it has been shown that those external factors which have most influence on the formation of glycogen by the liver, such as deficiency in the pancreatic functions, interfere extremely little with the process of polymerization of lævulose. This all goes to confirm Strauss's view that the cause of the alimentary lævulosuria of patients with liver complaints is to be sought in a pathological condition of the liver cells themselves (41). This ist he *insuffisance hépatique* of French authors.

In the other forms of pathological alimentary glycosuria it is necessary to assume an external influence acting upon the liver cells. It occurs to one at once that nervous factors may act thus, and one recalls to mind the results of experiments in connection with neuro-hepatogenous glycosuria. Moreover, alimentary glycosuria has been shown to occur in many nerve diseases. The latter may be either organic—such as progressive paralysis, multiple sclerosis, cerebral tumours, and peripheral neuritis—or functional—such as traumatic neuroses, mania, melancholia, hysteria, and commotio cerebri. It appears that, under the influence of the diseased nervous system, the diastatic processes are continually being urged to increased activity, so that the hepatic veins become swamped with sugar when any quantity of carbohydrate is given in the food. Our present-day knowledge, however, is insufficient to either prove or disprove the correctness of this assumption.

In other forms of pathological alimentary glycosuria the action of centrifugal nerve stimuli is much less probable. I have in my mind particularly severe febrile processes, acute and chronic alcoholism, and Graves' disease. These are affections in which alimentary glycosuria appears, not with absolute regularity, but still, much more commonly, and with much greater intensity, than in almost any others. Although the glycosuria is here transitory, I do not hesitate to observe an analogy to real diabetic glycosuria—that is to say, to seek the ultimate cause in pathological changes in the pancreas. It is true that anatomical research upon the pancreas in relation to diabetes mellitus has not yet carried us very far (*vide infra*); nevertheless, in continuation of the work done by Wille (41A) upon this point, it will well repay the trouble to examine the pancreas very carefully in every case in which, during life, considerable alimentary glycosuria has been observed. It is obvious that severe febrile processes may injure the parenchyma of the pancreas. The same possibility must be allowed in the case of acute and chronic

poisoning. As regards Graves' disease, inter-relationships of function between the thyroid gland and the pancreas are at least probable, even though one may not speak of them with such certainty as Lorand (41) does.

This by no means exhausts the whole list of diseases in which the pancreas must be allowed a possible part in pathological alimentary glycosuria. Klippel and Lefas, and Steinhaus (43), have mentioned, and Bleichröder (44) has partly confirmed, the fact that disturbances of the portal circulation may bring in their train secondary changes in the pancreas. Hoppe-Seyler and Herxheimer (45) regard arterio-sclerosis as a potent factor in causing degenerations in the pancreas. Most of these questions are open to study by experiments upon animals. Positive data are still too few to justify a more detailed discussion now. It is, however, surely more than coincidence that the tendency to alimentary glycosuria is greatest in high fevers, in severe alcoholism, and in Graves' disease, whilst it is precisely in these affections that the line of demarcation between alimentary glycosuria *e sacharo* and alimentary glycosuria *ex amylo* happens to disappear. I myself, on the first discovery of febrile alimentary glycosuria, found very large quantities of sugar excreted. Poll (46) found the same. My former assistant, Strauss (47), then pursued the question further, and found that, besides glycosuria *e sacharo*, a glycosuria could also be brought about by giving quantities of starch to alcoholic subjects, or to patients suffering from influenza or pneumonia. Glycosuria *ex amylo* has long been regarded as the typical sign of true diabetes [Naunyn (8) and Strauss (47)]; and here for the first time it had been produced in persons who, in the clinical sense, were certainly not diabetics, and who presented only a temporary disposition to glycosuria. In the light of the above observations we are bound to admit that the cases were really acute temporary pancreatic diabetes of slight degree, and due to an infective or to a toxic condition, as the case might be. I have since frequently seen glycosuria *ex amylo* in patients who were suffering from influenzal pneumonia, and who neither before nor since exhibited the slightest sign of diabetes mellitus. I have also seen it in a female who had Graves' disease.[1]

[1] I should like to give notes of this case here, because I do not know if I shall have an opportunity of doing so elsewhere, and because it seems to me to be one of great importance. The lady, then twenty-five years old, and single, began to suffer from the typical symptoms of Graves' disease in the spring of 1898. The condition developed rapidly, but did not become severe. There was obvious exophthalmos, enlargement of the thyroid gland; pulse 100 to 110; tremor, perspiration, wasting, and tendency to diarrhœa. In June, 1898, on six consecutive days at 8 a.m., and before breakfast, I gave her alternately 100 grammes of grape-sugar or 200 grammes of bread—white and rye bread mixed—with 300 c.c. of tea. On the three glucose days she excreted 6·7, 8·2, and 5·8 grammes of grape-sugar. On the three bread days she excreted 4·2, 5·1, and 3·8 grammes of grape-sugar. The glycosuria was each time over by midday. The Graves' disease got well within nine months. The lady meanwhile got married. She became the mother of several children. Repeatedly—the last occasion being in August, 1904—I tried to see if glycosuria could be produced by giving increasing quantities of bread, starch foods, and sugar. Sugar never recurred in the urine.

D.—DIABETIC HYPERGLYCÆMIA AND GLYCOSURIA.

1. The Amount of Glycogen in the Organs of Diabetic Subjects.

When, in attempting to explain diabetic hyperglycæmia and glycosuria, we glance at the carbohydrate metabolism of diabetic patients, one of the first and most important points to strike us is the poorness of the organs in glycogen. Lépine calls this " azomyelie "; Naunyn (48) terms it " dyszöoamyelie." Post-mortem observations upon the amounts of glycogen in livers vary much, but it is established that the liver has been found extremely poor in glycogen when the blood at the same time contained much sugar—in other words, when the liver normally would have had ample opportunity to load itself with glycogen [Naunyn (49)]. Frerichs, through P. Ehrlich (50), performed the ingenious experiment of puncturing the livers of two diabetics and one healthy man by means of a fine trocar during life. All were placed on similar starchy diet. The aspirated liver pulp of one of the diabetics contained no glycogen at all, and that of the other far less than was present in the case of the healthy man.

There are possible objections to conclusions drawn from autopsies notwithstanding Naunyn's belief that all such have been now removed. It is, perhaps, better to rely more upon the teachings of experimental pancreatic diabetes. In almost their earliest work von Mering and Minkowski (25) pointed out the extraordinary scarcity of glycogen in the liver in these cases.[1] This has been repeatedly confirmed, not only for the liver, but also for the muscles (50). Minkowski showed that it made little difference whether the animal had been allowed to fast, or whether it had been given quantities of starchy foods and grape-sugar before death. The blood was always rich in sugar, and the liver always poor in glycogen. The results found at human autopsies have not always been quite so marked. One cannot help thinking that, in man, even when death has resulted from coma, the diabetes has not always been quite " complete " — that is to say, the pathological processes which produce diabetes have not developed so far, and the factors which favour the storing up of glycogen have not been so completely removed, as is the case in a dog whose pancreas has been entirely ablated. Pflüger (52) has recently declared that the finding of glycogen in the liver and muscles at some autopsies on diabetic patients is a point of more importance than is the finding of none at all in other cases. For this view to be maintained it would be necessary to prove that the cases in question had really suffered from " complete " diabetes,

[1] Pflüger has recently carried out analyses in a dog which died from diabetes after complete removal of the pancreas. The liver was large, weighing 293 grammes, or 4·77 per cent. of the entire body-weight; it contained 0·0259 gramme of glycogen. Pflüger says: " This fact proves that the liver continues to form glycogen to the end, even in the severest cases of diabetes." This cannot be gainsaid, but the analysis shows more markedly still that the important function of glycogen formation was reduced to a minimum (50A). Of another dog, which also died of diabetes following total extirpation of the pancreas, Pflüger says: " The liver contained absolutely no glycogen at all " (*Pflüger's Arch.*, 106, 187, 1905).

analogous to the diabetes that follows thorough extirpation of the pancreas, and that the patients had died, not of complications, but of the specific disorder of metabolism in its last degree (compare Cases P. and K. below). Incomplete removal of the pancreas does not make the liver free from glycogen, as de Dominicis (53) has shown. In my own laboratory the following figures were obtained by the most reliable known methods at autopsies upon diabetic subjects :

1. Patient R. received 50 grammes of lævulose forty-eight hours before death, and thereafter took no more carbohydrate. The liver contained 0·06 per cent. of glycogen, the limb muscles traces, the diaphragm 0·7 per cent., the heart 0·4 per cent., the kidneys 0·1 per cent.

2. Patient J. passed rapidly from a state of well-being into coma, and died within a few hours. The autopsy was two hours later. The stomach was still full of food. The liver contained no glycogen, the muscles 0·1 per cent., the heart 0·1 per cent., and the kidneys 0·1 per cent.

3. Patient P. suffered from moderate diabetes, with slight acidosis and chronic dry gangrene of the toes. His diet was liberal, containing about 50 to 60 grammes of carbohydrate per diem. He died suddenly of pulmonary embolism. The liver contained 1·8 per cent. of glycogen, the muscles 0·4 per cent., the heart 0·7 per cent., the diaphragm 0·4 per cent., and the kidneys none.

4. Patient K. suffered from diabetes of medium severity, complicated by pyæmia and severe nephritis. He died of uræmia. The liver contained 0·3 per cent. of glycogen, the psoas muscles traces, the pectoral muscles 0·03 per cent., the diaphragm 0·03 per cent., and the heart 0·3 per cent.

5 and 6. Patients W. and S., severe cases of diabetes, who died from coma. Both women partook of considerable quantities of lævulose within twenty-four hours of death. Analyses for glycogen showed :

	Liver.	*Muscles.*	*Heart.*	*Diaphragm.*
	Per Cent.	Per Cent.	Per Cent.	Per Cent.
W.	2·5	0	—	—
S.	2·5	Traces	Traces	Traces

We thus found quantities of glycogen only in those cases where death was not directly due to the diabetes, or else where lævulose was given within a short time of death. In the latter cases the liver alone was rich in glycogen. The same distribution of the glycogen appears when animals have first been made glycogen-free by strychnine, and have then been fed plentifully with carbohydrate.

Physiology teaches us that certain places are normal depots for glycogen. In diabetes other cells also have the power to store up glycogen—for example, the renal epithelium (54), pus corpuscles (55), and possibly also the leucocytes of the circulating blood (56). The cells of

Henle's tubules constantly store up glycogen in this way; Weigert never failed to find this to be so in numerous autopsies upon diabetics. Probably this accounts for the traces of glycogen which have sometimes been detected in diabetic urine [W. Leube (57)]. It is clear that the cells in question—renal epithelium, pus corpuscles, and leucocytes—take up a larger quantity of glycogen than usual on account of the hyperglycæmia. We lack the biological explanation as to why certain cells retain this function, and even exert it more actively than before, whilst the proper organs for the storage of glycogen have lost it.

The amount thus stored up, however, is too small to be of great importance for the maintenance of the necessary amount of carbohydrates in the tissues.

2. Defective Combustion of Sugar.

We can only give a conditional affirmative answer to the question whether the inefficiency of the normal glycogen depots is the right explanation of the disturbances that occur in diabetes. It accounts for the flooding of the blood with sugar, whether the latter comes direct from the intestinal canal, or is formed by katabolism from proteid, and possibly from fat and other substances. The tissues will not consume a larger quantity of material than is required for their respective energies. If the glycogen depots are no longer active, the sugar which is not used up in the performance of work, or in the production of fat, remains in the blood and tissue juices, and is removed by the kidneys. All the variations in diabetic glycosuria which follow upon changes in the diet are satisfactorily explained upon this view, notwithstanding the extraordinary differences such changes in diet produce in different cases and in different stages of the disease (*vide infra*). In the majority of cases the glycogenic function is not in complete abeyance, but is only defective to a greater or a less degree.

A difficulty, however, at once arises. If defective glycogen storage were the sole cause for the glycosuria, the latter should be greatly affected by variations in muscular work. The muscles, whose energy in health is supplied by carbohydrate, should utilize a larger quantity of the circulating sugar when they do more work, and leave proportionately less for the kidneys to excrete. It is of course well known to every physician that diabetics can tolerate slightly larger quantities of carbohydrate when they take fairly active exercise, and for that purpose are sent to the hills. This is of great importance from a therapeutic point of view. The favourable effects come on gradually, and no doubt depend upon increase of musculature by physiological hypertrophy, and upon other good influences which an open-air life has upon the patients. The fact that moderate exercise may sometimes cause decreased elimination of sugar in the urine is undoubted. It is seen most clearly in slight degrees of diabetes when the muscles are not quite free from glycogen. In severe cases the results are much less obvious. I have made many observations upon this point, sometimes with the ergostat, sometimes with hill-

climbing. The diet both on rest days and those of work was kept the same both as to quantity, quality, and the times of taking meals. In the healthy man a good measure of the sugar katabolism in the muscles is afforded by the heat-production expressed in calories. On the work days the calories of heat stood at a far higher figure than on the rest days, and yet in many diabetics the glycosuria diminished little, if at all. I shall give several examples of this in a later section of this chapter. I have even met with cases where muscular exertion actually increased the glycosuria (58).

Very great importance must be attached to the above observations. They show that the sugar circulating in excess in the blood is of little or no use to the cells for katabolic purposes.

The same conclusion may be drawn from researches upon the respiratory exchange of diabetic patients. When a healthy man is fed upon carbohydrate, his respiratory quotient immediately rises nearly to 1. The same is not the case in a diabetic. Even when fasting his respiratory quotient is strikingly low, showing that his combustion of carbohydrate is much below normal. Administration of starchy foods or grape-sugar raises the quotient little, if at all (see next page).

Some observers have sought to demonstrate the non-utilization of the circulating sugar by comparisons between the arterial and the venous blood. Lépine and Barral hold that less sugar disappears from the blood of depancreatized than of normal animals (59). Chauveau and Kaufmann (60) deny this. It is unwise to lay much stress upon any experiments of this kind, seeing that the technical difficulties render them very unreliable.

The facts as a whole show that the body cells, particularly those of the muscles, can make but imperfect use of the sugar, although this is flowing through them in abundance. All the relations between defective glycogen storage and glycosuria become clear if we adopt the hypothesis that the carbohydrate of the cells—at any rate, in diabetic subjects—cannot be properly katabolized because it is not first fixed in them as glycogen. Looked at from the point of view of general biology, there is no objection to this assumption, which was strongly advocated by Seegen (61), and again recently by Naunyn (62). It is certainly not the substances in which the cells are bathed that are the immediate source of energy; the food-stuffs must become chemically anchored to the cells before further katabolism is possible.

We are now about to enter upon very difficult theoretical ground. There can be no doubt that every point which has been brought forward in favour of the non-combustion of sugar in the muscles is capable of a different interpretation, if we depart from the very probable assumption that only carbohydrate, and not fat or protein, can be directly used by muscle in the performance of work. One might then hold that the muscles katabolize just as much carbohydrate as usual, but that they have lost the power of storing up reserves, whilst retaining the power of calling by chemical signals for more sugar from the liver. This chemical stimulation of the liver might even be increased in direct proportion to the deficiency in the glycogen-storing power. Hyperglycæmia would be the

immediate result. This hypothesis affords an equally good explanation of the facts we have mentioned above in regard to the respiratory quotient.[1]

3. Utilization of Lævulose.

I put forward the last paragraph merely as a hypothesis, for there is no direct proof that glycogen formation is an indispensable preliminary to carbohydrate katabolism in muscle. There is, indeed, a very important piece of indirect evidence to the contrary. Külz (63) long ago discovered that lævulose is incomparably better borne by diabetics than are grape-sugar and starches. Bacterial biology affords an analogy. *Saccharomyces ellipsoideus* assimilates only the dextro-rotatory mandelic acid, and in a mixture of these acids leaves the two lævorotatory varieties alone [Bunge (64)]. The diabetic subject, one might think, may have lost the power to assimilate the dextro-rotatory, but may have retained the power to assimilate the lævorotatory sugar. The analogy fell through when Minkowski (65) showed that much glycogen can be stored up when lævulose is given to animals suffering from pancreatic diabetes. A dog in this condition received 400 grammes of lævulose during the three days preceding its death. Some 200 grammes were excreted in the urine, mostly in the form of grape-sugar; in the liver there was 8·14 per cent. of glycogen, and in the muscles 0·81 per cent., making a total of about 90 grammes.

In the face of these facts it is no longer possible to maintain that diabetics are able to katabolize lævulose directly. The only conclusion that can be safely drawn seems to be that diabetics are able to form glycogen from lævulose within certain limits, and that their cells can utilize this in the usual way in performing work.[2] In order to understand the facts observed after feeding with lævulose, the mechanism here at work must be explained rather more fully. Part of the lævulose which flows in the portal vein from the intestine to the liver becomes fixed as glycogen in the latter. Except in so far as this glycogen is used locally for the work done by the liver cells and for the formation of fat, diabetic patients can make no use of it, for this glycogen is returned by the liver to the blood as dextrose, and is of as little use as if given as dextrose in the first instance. Part of the lævulose, however, passes through the liver. A certain amount may be eliminated in the urine, and when much lævulose is given in severe forms of diabetes this is the rule. Some, however, is taken up by the muscles, is there polymerized into glycogen, and utilized. This is the explanation both of the fact that diabetic

[1] N. Zuntz (*Berliner Physiol. Gesellsch.*, June 22, 1894) brought forward definite proof that muscular work can be done by katabolism of protein, of fat, and of carbohydrate. Thus far Zuntz confirmed the results of former metabolic researches and calculations. Nevertheless, Zuntz did not prove that muscle protoplasm can itself utilize protein and fat just as well as it can carbohydrate. Much more likely is it that carbohydrate is first formed elsewhere in the body from protein and fat, and that the blood carries this carbohydrate ready prepared to the muscles [von Noorden (62A)].

[2] That lævulose can be converted into dextrose in the animal body has long been known. Von Voit (60) first suspected, and Minkowski first showed, it to be probable, that one way of doing this was via glycogen. Whether or not this is the only way is still an open question.

patients metabolize lævulose better than they do dextrose, and of the fact that after administration of lævulose there may be much glycosuria but little lævulosuria.

It is not every diabetic subject who can thus utilize lævulose better than dextrose. The condition is not constant even in the same individual. Long-continued feeding upon lævulose leads to impairment of its assimilation. One example out of the many cases that I have watched will indicate what I mean :

A female patient, aged twenty-eight, who died some two years after the following observations were made, was put upon a strict and fixed diet, to which were added various quantities of bread, dextrose, and lævulose. The urine at that time never contained more than 0·1 to 0·2 gramme of acetone in twenty-four hours, and gave no ferric chloride reaction.

Day of Observation.	*Additions to the Fixed Diet.*	*The Twenty-four Hours' Urine contained—*	
		Dextrose.	Lævulose.
		Gm.	Gm.
1	—	18·3	—
2	—	21·6	—
3	—	17·3	—
4	100 grammes rye bread	42·5	—
5	,, ,,	48·3	—
6	,, ,,	56·1	—
7	,, ,,	54·8	—
8	50 grammes glucose	54·7	—
9	,, ,,	58·2	—
10	,, ,,	56·0	—
11	,, ,,	40·5	—
12	,, ,,	35·2	—
13	,, ,,	32·0	—
14	50 grammes lævulose	28·6	(?)
15	,, ,,	30·3	(?)
16	,, ,,	40·7	5·2
17	,, ,,	42·6	8·1
18	,, ,,	43·1	8·1

The observation was interrupted by the onset of menstruation on the fifth day of giving lævulose. The latter was stopped because it appeared to have no particular advantage over the ordinary bread. From this and other similar determinations it appears to me probable that the power to form glycogen from lævulose becomes rapidly exhausted in severe cases of diabetes. It would be well worth while to carry out further exact researches upon this point.

4. Relationships between Glycogen Formation and Diabetic Glycosuria.

If the above conclusions be correct, then all food-stuffs, whether carbohydrate or not, which prove to be producers of glycogen after extirpation of the pancreas must increase the glycosuria of diabetics

to a much less extent than do grape-sugar and starch. It is not so much the formation of glycogen in the liver as that in the muscles which is here concerned.

Hitherto very little has been found out with certainty in regard to the rôle of the liver in this respect, and practically nothing in regard to that of the muscles.

The converse would be that substances which lead to glycogen formation in healthy people, but which cause no storage of glycogen after extirpation of the pancreas, must increase diabetic glycosuria. That this is so has not been established. It would entail the premise that the body possessed no other way of storing carbohydrate than that via glycogen. It is only in the case of dextrose and lævulose, and even then only as far as metabolism in the liver and muscles is concerned, that we possess any evidence to justify such an assumption. It is possible that the carbohydrate which is formed from the amido-acids of the protein molecule may be governed by quite different rules. The carbohydrate molecule here arises within the cells themselves, and may perhaps—*in statu nascendi*, or after becoming linked to other molecules—become katabolized by the cells of the diabetic patient without ever becoming transformed into glycogen. We have far too little knowledge to be able to go into these questions in detail. The peculiarities which have to be reckoned with are shown, for example, by some work of Lüthje's (67), from which it appears that tissue protein is katabolized differently to food protein. The katabolism of the former increases the glycosuria far less than does that of the latter. Perhaps the old hypothesis, recently revived, that fatty acids must be converted into carbohydrate before being oxidized in active muscles may presently be verified. If so, it would be unlikely that glycogen is an intermediate step, for no one has yet been able to demonstrate glycogen formation from fatty acids, though there are many points in favour of the view that fatty acids are capable of producing sugar.

These theoretical discussions show how much work is yet to be done. If we now return to the main question, the most probable answer seems to be :

The power of converting grape-sugar into glycogen has been lost by the diabetic subject in a degree varying with the severity of the case. Under certain conditions the same applies also to lævulose. Hence the physiological depots of glycogen become empty, and there is defective combustion of sugar because the muscles cannot polymerize the sugar which reaches them in the blood-stream.

5. Defective Formation of Fat from Carbohydrate.

It is an important rôle of healthy organs to synthesize fat from the carbohydrate which is not at once used up or converted into glycogen. When carbohydrate metabolism is out of order, not only is there difficulty in katabolizing sugar into CO_2 and water, but the synthesis of fat is disordered too (68).

If the oxidation of carbohydrate were alone defective, it could not lead to persistent and severe glycosuria upon a diet in which carbohydrates were much restricted. Upon such a diet the total quantity of new-formed sugar is comparatively small, and certainly reaches nothing like the amount which a healthy man upon full diet absorbs and utilizes. The carbohydrate not required in the muscles and glands, and so forth, should be taken up by fat cells and converted into adipose tissue, as it is in health. Hyperglycæmia and glycosuria can only result when the sugar molecule has become inaccessible to the fat-forming as well as to the oxidizing cells. It is possible that the fat-forming process depends upon glycogen formation as much as does the process of oxidation ; but of this we have no certain knowledge.

It seems to me that the following idea is worth consideration : One might suppose that there are patients in whom only the power of katabolizing sugar is wanting, the synthesis of fat still being carried on. Under these conditions the active body cells would be bathed in fluid rich in sugar, but would none the less fail because they could seize upon the sugar molecule either with difficulty, or not at all. A sort of tissue hunger would result, leading to a reflex increase of appetite and corresponding food consumption. The latter would lead directly to a laying-on of fat.

Such people would be suffering from sugar disease, but would not eliminate any sugar in the urine. They would become obese. The " fat disease " would mask the diabetes. The condition would be one of " diabetogenous obesity," as I must call it, in contradistinction to the usual doctrine of " lipogenous diabetes."

The above conception brings us to the following clinical schema:

1. There are cases in which the combustion of sugar and its conversion into fat are simultaneously defective ; glycosuria of various degrees, with wasting ; ordinary diabetes.

2. There are cases in which the combustion of sugar, but not its synthesis into fat, is defective ; obesity without glycosuria ; masked diabetes. These cases readily develop at a later date into—

3. Cases in which the combustion of sugar is defective, and the heaping-up of carbohydrate in the form of excessive fat also begins to fail ; obesity with subsequent glycosuria ; ordinary diabetes of fat people.

By going one step further cases of Group 3 become cases of Group 1.

I regard this theory as well justified, though there are many gaps in our knowledge which can only be filled by hypotheses. Von Leube, Krehl, Pflüger (69), agree with me. B. Naunyn (70) alone raises objections. He recognises the defective formation of fat, but does not attribute it to any actual anomaly of metabolism. He thinks that the formation of fat from the hexose molecule is not sufficiently rapid to keep the percentage of sugar in the blood at its normal low level. The sugar drains away in the urine before it can be transformed into fat. The defective formation of fat is, in Naunyn's opinion, a question merely of the time the process takes. To this it must be objected that nothing whatever is known about the time necessary for fat formation, and that, in comparison with a person on antidiabetic diet, a healthy man, fed up

with carbohydrate, deals with very much larger quantities of carbohydrate in a given time, and stores it up as fat.

Whether my explanation or Naunyn's is correct, or whether both must be changed for another, cannot be decided to-day. There can, however, be no difference of opinion as to the fact that fat formation is disordered in many diabetic patients.

6. Overproduction of Sugar.

In addition to defective sugar combustion, an increased sugar production has always figured largely in all theories of diabetes. Many difficulties surround this question, because so little is known about the normal production of sugar. The whole matter is in a tangle, and can only be aprpoached in a roundabout way. We could be certain of an overproduction if we knew of any substances which did not lead to the formation of sugar in health, but did so in diabetes. Even then it would be necessary to inquire whether the overproduction was primary and fundamental, or whether it was secondary, and due to the draining away of sugar and to the carbohydrate hunger of the tissues. The view that it is secondary seems to hold good in phloridzin diabetes.

Carbohydrates themselves can hardly be expected to be a source of overproduction. It is their normal part to be transformed into sugar. Any excess is synthesized into fat by the tissues, particularly by the liver, and perhaps also by the connective tissues [Rosenfeld (80)]. Glycerine must be ranked with the carbohydrates. The part it plays in connection with fat metabolism in diabetics is very important (see below). It is at least probable that sugar can be formed from it [Külz, M. Cremer, Lüthje (81)]. Lecithin, which contains glycerine, must also be mentioned here [Lüthje, Mohr (82)].

(*a*) *Sugar from Protein.*

The question is much more difficult when protein is considered. From the chapter upon Glycogenesis it will be remembered that it is from the metabolism of diabetics that weighty evidence has been drawn as to the origin of sugar from albuminates. The conclusions rest upon the facts that diabetics with severe glycosuria continue to excrete far more sugar than is contained in their restricted diet, and that very often their increase in glycosuria can be shown to be approximately proportional to any increase in the intake of protein. The classical work of Naunyn, von Mering and Külz (83), has made the question of the formation of sugar from protein a regular basis for researches in physiological chemistry (see references 84, 88, and also Vol. I.). Several newer observations, partly clinical, partly experimental, confirm the older doctrine. Pflüger, too, who is a severe critic of all the work that has been done, inclines to support it. He lays particular stress upon the important evidence afforded by some researches of Lüthje's (85A).

The simplest way for a physician to convince himself of the formation of sugar from protein is for him to put a diabetic patient for some days upon a diet containing little protein and almost no carbohydrate. The sugar in the urine falls to a minimum. If albuminates be now added to the diet, the amount of sugars still remains low in many cases. The patient has developed some degree of tolerance, as the result of simultaneous decrease in both protein and carbohydrate—a fact well worthy of attention from a therapeutic point of view. In particularly bad cases, however, the sugar quickly rises again as the albuminates are increased. I select the following instance from among a great number I have watched :

Day.	*Diet.*	*Sugar.*	*Remarks.*[1]
		Gm.	
1	Ordinary strict diet	48·2	The sugar was estimated in the urine by Soxhlet's method.
2	,, ,, ,,	56·7	—
3	,, ,, ,,	57·1	—
4	Vegetable diet	30·2	—
5	,, ,,	11·9	—
6	,, ,,	2·1	—
7	Vegetable diet + 300 grammes meat	7·8	The figure " 300 grammes " represents the weight of the meat raw.
8	,, ,, ,,	22·8	—
9	,, ,, ,,	33·5	—
10	,, ,, ,,	36·7	—
11	,, ,, ,,	42·3	—
12	Vegetable diet	8·1	—
13	,, ,,	A trace	—

In some cases the difference between the vegetable and the meat days in regard to the sugar in the urine is even greater. Every physician who has had diabetic patients under his care has observed the same. Clinicians are unanimous in believing that sugar can be formed from protein. Pflüger raises objections to the evidence of such observations. He thinks diabetic patients are not to be trusted. He ventures the suggestion that, longing for bread, as these people always are, they may have been surreptitiously supplied with carbohydrate at the critical moment. In making such an objection the physiologist is underestimating the scientific powers of the physician and the will-power of the patient, who is keenly interested in what is for his own welfare.

Pflüger, however, does allow that sugar can be produced from protein to a limited extent—namely, in so far as the carbohydrate is contained preformed in the protein molecule. He refers to the thesis written by

[1] On the vegetable diet days 400 grammes of asparagus were eaten for breakfast ; at midday and at supper there were alternations between spinach, sauerkraut, green French beans, green haricot beans, and lettuce. In addition to these, there was a daily allowance of two salted cucumbers of medium size, the yolks of seven eggs, 60 to 80 grammes of bone-marrow, 50 to 60 grammes of pure lard, and unlimited butter—a total of about 200 grammes of fat per diem. Black coffee, tea, lemon-squash, and strong beef-tea in small quantities were the fluids given.

him long ago, and maintains that the protein nucleus combines with carbohydrate to form a sort of glucoside, but that the carbohydrate constitutes no integral part of the protein molecule. This conception of the glucoside nature of many proteids has been thoroughly established. We discussed the matter fully elsewhere in this work. I would also refer the reader to the important researches of Kossel, Pavy, Müller, Krawkow, Blumenthal and Langstein (87), and to the excellent list of further references given by Langstein (88). There are, however, weighty arguments against the preformed sugar of the proteid-complex being the only source of sugar from protein. Casein, which of all protein stuffs is the poorest in preformed carbohydrate, is a very potent producer of sugar in cases of diabetes (89) [Lüthje, Falta, von Noorden, Mohr, Therman (89)].

Cohn and Müller (90) have drawn attention to another atom-complex of the protein molecule as a possible source of sugar—namely, the amido fatty acids. Leucin, which is the first to occur to one's mind, has not yet been absolutely proved to be convertible into sugar (91); but an observation made in my wards by Mohr (92) renders the origin of sugar from it very probable. On the other hand, it has been definitely shown that alanin can give rise to glycogen in non-diabetic, and to sugar in diabetic animals (92). The same has been shown for asparagin (93) and for glycocoll [Embden and Salomon].

Fed Substance.	*Sugar—*		
	Before Feeding.	Day of Feeding.	Day after Feeding.
	Gm.	Gm.	Gm.
Alanin	16·00	29·30	19·30
Alanin	6·20	19·50	3·60
Asparagin	1·70	8·48	2·45
Glycocoll	1·79	10·05	2·45
Glycocoll	2·45	5·26	7·00
Glycocoll	2·45	7·90	3·00
Alanin	2·50	18·00	6·20

The above are Embden and Salomon's figures. Mohr (93A) obtained similar results with alanin, asparagin, and glycocoll. Benzoic acid diminished the glycosuria of dogs suffering from pancreatic diabetes. Perhaps the benzoic acid takes up some of the glycocoll, and prevents it from taking part in the formation of sugar.

In view of these careful proofs that such constituents of protein are really sugar-producers both in non-diabetic and in diabetic subjects, Pflüger's principal objections to the production of sugar from protein fall through. None the less, we must be extremely grateful to this observer for his minute and careful criticism of the earlier work upon this subject—criticism which has made it easier to avoid errors in subsequent researches. His own very exact observations upon feeding dogs suffering from pancreatic diabetes with cod and with nutrose free from glucoside are at least not incompatible with the formation of sugar

from protein, although it must be granted that the results might equally well be explained by the formation of sugar from fat (94).

It is of very great importance, from the point of view of diabetes, to know with certainty how much sugar can be formed from protein. Each variety of protein must be investigated separately as regards this point. Neither the amount of loosely-combined carbohydrate, nor the quality and quantity of the amido-fatty and other acids in the protein nucleus, nor, perhaps, the intrinsic sugar-forming groups which we expect to discover in the future, are the same in all protein. Numerous researches have been carried out. The question is all-important, not merely for the theory of diabetes, but also for the dietetic treatment of the condition. Different forms of protein have been given, one at a time, to diabetic patients by Lüthje, Stradomsky, Schuman-Leclerq, Falta, Mohr, and Therman (95). The observations are extremely difficult to carry out, and still harder to draw conclusions from. They must extend over a considerable time. The tolerance of diabetic patients may vary spontaneously, and within wide limits, during the experiments. It is not to be wondered at that the results have not been uniform. It seems to be a general rule, however, that vegetable proteins and egg-albumin, which are particularly rich in glucoside sugar, have the least tendency to evoke glycosuria, whilst meat protein and casein, both of which contain little glucoside, increase the glycosuria to a considerable extent. Every form of food protein causes more glycosuria than does the breaking-down of tissue protein [Lüthje (67)]. I must add that my own clinical and experimental experience is that, in addition to variations in the quality of the ingesta, there are undefined personal factors in each individual diabetic which greatly modify the results. This is very clearly seen in the case of vegetable protein, which is usually born well in comparison to egg-albumin, and very well indeed compared to meat protein, and yet sometimes gives the worst results.[1] Falta has observed the same in cases fed upon casein.

It is probable that other factors besides the varying amounts of glucoside sugar and of sugar-forming amido-fatty acids in the different kinds of protein are of importance in the effects the latter have upon the glycosuria. The time is not yet ripe for discussing these. Falta (95) has drawn attention to a series of questions upon which it is to be hoped that research will be made in the future. He points out, for example, the great difference there is between casein and egg-albumin as regards rapidity of katabolism. Egg-albumin is broken down much the more slowly. Perhaps this helps to explain its slighter influence upon glycosuria.

Kraus (96), using the knowledge that a sugar can be formed from amido-acids, has endeavoured to find out whether the tissue protein of an animal which is thus forming sugar from albuminates becomes depleted of amido-acids. As Kraus points out, there might in this way arise " a partial deterioration of the chemical type." He found that mice which

[1] There is an observation of Mohr's which bears upon this point (82). My observations upon the action of vegetable protein were made partly with Roborat, partly with a rice proteid from Bremer's bread manufactory, partly with a wheat protein which was supplied to me in bulk from Hoffmann's starch works.

had succumbed to phloridzin diabetes contained less monamino-acid nitrogen than normal, and particularly less leucin, in proportion to the total protein in the body. Perhaps his methods were not free from objection, and his results may not be conclusive [Abderhalden, Bergell, Dörpinghaus (97)] ; but he has opened up a line of research which should be very fruitful. Pflüger found that the total nitrogen and total ash residue showed no departure from normal in a dog which died of pancreatic diabetes. He does not at all incline to any theory which assumes an alteration in the intrinsic nature of the proteids in diabetes (97B).

Magnus-Levy (98) has approached the queston of sugar-production from protein in a no less original way, and from quite a different side. He calculated what the respiratory quotient of a diabetic patient should be if he supplied the oxidation processes entirely from fat and albuminates free from carbohydrate. The figures would lie between 0·706 and 0·613. This is what is actually found in severe cases of diabetes, as Magnus-Levy points out. Pflüger's (97A) criticism of these calculations seems to me to go too far. Even if we must accept Pflüger's objections upon many points, upon this one they do not seem to be valid.

It must, therefore, be allowed that severe cases of diabetes do form some sugar from protein. We do not know, however, to what extent this can occur. Until quite recently the general view was that almost the whole of the nitrogen-free residue of the protein molecule was converted into carbohydrate previous to oxidation. Landergren (99) disputes this. He states that the production of glycogen or sugar from protein, apart from the mere splitting off of the preformed carbohydrate, is only a last resort—that is to say, it only occurs when there is no other carbohydrate whatever at hand. If this be correct, such a process of sugar-formation must be regarded as abnormal even in diabetes, and the overproduction of such sugar would be truly secondary.

Should this necessity for sugar-formation from protein arise, the maximum proportion of such sugar to protein nitrogen should theoretically be 8 : 1 [von Mering, Landergren (100)]. The ratio $\frac{D}{N}$ (*i.e.*, dextrose to nitrogen) has figured largely in the literature upon this question, since Minkowski (53) showed that in dogs suffering from diabetes following upon total ablation of the pancreas a diet completely free from carbohydrate usually rendered the urine quotient $\frac{D}{N}$ 2·8 or less. Minkowski concluded, from the constancy of this quotient, that this may be the ratio in which the body tissues produce sugar from protein. He assumed, however, that an animal without a pancreas can no longer utilize any sugar at all, and that all the sugar that might be produced would appear in the urine. This assumption is certainly not justified, as Lüthje (101) shows. Moreover, both in experimental phloridzin diabetes (102) and in human diabetes mellitus (102A) much higher quotients have been met with, approaching more nearly to the theoretical maximum of 8 : 1, and even exceeding this (see below). Moreover, even after total extirpation of the pancreas, both lower (94) and higher figures have been obtained (51).

Fresh discussion upon the quotient $\frac{D}{N}$ has recently been aroused by Pflüger and Minkowski (101A). The latter maintains that in dogs suffering from experimental pancreatic diabetes this quotient is, upon the average, 2·8 with remarkable constancy, though there may be considerable daily variations. The constancy of this average, however, cannot be held to justify the interpretation which Minkowski originally gave it.

It is only under particular circumstances that the figures have been anything like constant. In an extreme degree of phloridzin diabetes the quotient is 4 to 5 : 1. It is, of course, assumed that the diet contained no carbohydrate. If it contained any, the amount must be deducted from the total sugar in the urine before the ratio D : N is calculated. Neither from these, nor from the much higher figures afforded by human pathology, can any definite conclusion be drawn as to the ratio D : N giving any clue to the proportion in which sugar is yielded by protein. It is *a priori* very improbable that all the various atom-complexes of the protein molecule, after removal of the carbon necessary for the formation of urea, etc., should pass through a carbohydrate stage in the process of katabolism. It appears certain that this is not the case under normal conditions [Landergren (99)]. In severe diabetes it would seem that it only takes place when absolutely no other material is left upon which to carry on the various bodily functions. To explain so high a $\frac{D}{N}$ quotient as 8 : 1 in this way would only be justifiable if it were absolutely certain that there was no other source of sugar left in the body except preformed carbohydrate and protein.

(*b*) *Sugar-formation from Fat.*

There is much more evidence that fat can be a source of sugar-production. Against such a view Naunyn and von Mering have brought forward the facts that the giving of fat neither increases the hepatic glycogen of a healthy animal, nor increases the glycosuria of a diabetic animal or man. That the latter point is true has been long established clinically (102B). Exact research upon the point has been carried out by Weintraud, Hirschfeld, Lüthje, Schwarz, and Hübner (102C). I have myself confirmed the results, having made many exact observations upon the effects of giving maximal quantities of fat—up to 300 or 400 grammes—per diem. Details of these experiments are given by my pupils [von Lengyel, Mohr, and Loeb (102D). Loewi and Schmid (103) found the same thing in phloridzin diabetes, and Minkowski (53) in experimental pancreatic diabetes in dogs.

It has been proved that glycerin, a constituent of fat, can produce sugar. The next question is whether or not sugar can also be formed from the fatty acids.

The objection that is based upon the results of experimental feeding with fat can be disposed of at once. No increase in the glycosuria could be expected to follow increased fat consumption unless this additional

supply of fat caused increased fat combustion. This, however, is not the case. The conditions here are altogether different to what they are in the case of protein, increased administration of which is directly followed by its increased katabolism. The amount of fat broken down by diabetics is approximately the same whether much or little be given. The only difference would be that in the former case the material katabolized would be that just absorbed from the food ; in the latter case, that previously stored up in the body. My pupil, Rosenqvist (102A), gives a clear account of this. Pflüger (104) has recently expressed the same opinion, and obviously without being acquainted with Rosenqvist's work.

A second objection must now be met. There is no known chemical equation for the development of sugar from fat, and no one has yet succeeded in obtaining sugar, or even sugar-like bodies, from fatty acids *in vitro*. It is well known, however, that the reverse change can readily be brought about by the living organism. If the conversion of atoms can and does occur one way round, then by Hoff's law their conversion in the reverse direction must be possible. The phenomena of botany serve as an example. Plants form sugar from fat with great readiness. Pflüger (104) has even evolved a chemical equation by which this conversion may occur. Seeing, moreover, that the formation of sugar from amido-fatty acids has been definitely proved, it would be the extreme of obstinacy not to allow the possibility of sugar-production from fat itself.

Recent researches, carried out in my laboratory by Embden, Salomon, and Schmidt (104A), have thrown considerable light upon the chemistry of the process. These observers showed that the aliphatic monamino-monocarbon acids, which are derived from the protein molecule in the body, are broken down into fatty acids, and then suffer the same fate as do the other fatty acids. A bridge is thus thrown across between the two opposing camps, of which the one holds out for sugar-formation from protein, or, at least, from the amino-acids of albuminates, the other for sugar-formation from fatty acids. Among the katabolic products, both of the fatty acids, of the protein amino-acids, and of lactic acid (which beyond doubt leads to the formation of sugar), the same bodies occur—namely, acids containing two atoms of carbon, which are perhaps the most important of all immediate sources of sugar within the body. Further researches upon this subject are in progress.

There is a third objection. It has been maintained that in all known instances, provided there be no carbohydrate in the food, the nitrogen-free residue of the protein molecule is sufficient to account for all the sugar that appears in the urine ; more than sufficient if the glycerin derived from the breaking-down fat is counted in as well. It may be rejoined that, clinically, Rumpf, Rosenqvist, Mohr, and A. Hesse (105) often found six to eight times more sugar than nitrogen excreted in the urine. Those who oppose the doctrine that fat can form sugar (106) must in these cases assume that the whole of the nitrogen-free protein residue passes through a carbohydrate phase during its katabolism. This, however, is an uncalled-for hypothesis, and one which, as we have seen, is not even probable. In some cases [Mohr, Ascoli (107)] the quotient $\frac{D}{N}$

rose beyond the critical point 8, so that the explanation will not hold good, and other sources of sugar must be sought for. In one case of Lüthje's, mentioned by Pflüger (107A), the quotient rose as high as 14·6.

Umber (108) has raised a fourth objection, which appears more weighty. He calls attention to the fact that the protein molecule, when it begins to undergo katabolism, need not be disintegrated into the end-products of metabolism all at once. It is possible that the katabolism may be partial, or at least gradual. If this were so, sugar-forming chains might be split off first, leaving behind the atom groups which contained nitrogen. The nitrogen in the urine would then be no measure of the amount of protein which in any given time is helping to form sugar. The quotient $\frac{D}{N}$ would lose its significance, and equally so whether the nitrogen deficit came about from incomplete protein katabolism, or whether it were due to defective elimination of the nitrogenous end-products of metabolism. Consequently many authors [Lüthje, Hesse, Loewi, Langstein, Landergren] see no necessity for attaching any great importance to very high $\frac{D}{N}$ quotients, or for concluding from them that fat must also be a source of sugar. None of the researches carried out up to the present (102A, 105) serve to allay this objection entirely, although there are a few observations here and there, such as those of Mohr's (102A), which render it difficult to maintain. Personally, I regard Mohr's work as good evidence against the objection, notwithstanding Landergren's criticisms, but I quite agree that further observations must be made. It is not easy to make them. The number of cases of diabetes in which the excretion of sugar is so excessive is small. It is very difficult, with patients who are so ill, to carry out a long series of observations such as are desirable to ensure certainty in the results. The objections raised by Umber and others can only hold good over comparatively short periods.

The net result of researches so far has been to show that the critical value $\frac{8}{1}$ for the quotient $\frac{D}{N}$ is mainly theoretical, and that the actual findings exhibit wide variations. The production of something like 4·4 parts of carbohydrate from 1 part of protein may be regarded as to some extent proved [M. Rubner (109)]. All higher estimations seem to be accidental coincidences.

We shall only give a brief mention of the attempts to prove sugar-formation direct from fat which are based upon estimations of the total carbohydrate before and after liver emulsion, blood, etc., have been incubated along with fat or fatty acids. Some observers, such as Seegen, Weiss, and Bunge (110), find positive results; others, such as Zuntz and Cavazzani, Mortuori, Jacoby, Abderhalden, and Rona (111), negative. The question must be left open. One might expect that experimental transfusion of liver and muscles would yield more conclusive results. Positive findings alone could be admitted as evidence. Sugar-formation from fatty acids is certainly a very complicated process. Surviving organs

may no longer be in condition to complete the necessary syntheses and dissociations, which may be easy enough during life. Some transfusion experiments that Embden and Claus undertook in my laboratory were entirely negative as regards sugar-formation from fatty acids.

Observations upon the respiratory quotient are equally inconclusive. Cremer (112) has shown that the older observations were defective. More recent and well-designed experiments made by Lusk (113) merely show that administration of fat causes no increase of fat katabolism in diabetic subjects. No fresh light is thrown upon the question of sugar-production from fat.

A fact observed by Bouchard and Degrez (114) is noteworthy. When they gave large quantities of fat to animals suffering from extreme phloridzin-poisoning, glycogen became increased, not in the liver, but in the muscles. They concluded that the muscles form carbohydrate from fat. There are many objections to such a conclusion, but their aspect of the case is of sufficient interest to stimulate fresh experiments upon it.

To sum up, there is no conclusive proof that sugar can be formed from fat. It must be allowed, however, that since the year 1893, when I again raised the question which had lain dormant since Seegen's inexact and inconclusive experiments, and when I brought forward new points for consideration, my own views upon the formation of carbohydrate from fat have been favourably supported, particularly through the influence of Pflüger (104). I then described the formation of sugar from fat as "facultative." I meant by this that fat need not always, nor even as a rule, follow this line of katabolism, but that in case of necessity —that is to say, when there is no supply of ordinary carbohydrate to hand, and when the carbohydrate derived from albuminates is insufficient to cover the needs of the body, then fat can be utilized for the formation of sugar. Landergren (99) now speaks in similar terms of the formation of sugar from protein. Whether we must thus limit our views, or whether sugar-formation from fat is a regular daily process in health, are questions for the future to decide.

(c) *Secondary Overproduction of Sugar.*

If we now return to the question whether or not overproduction of sugar may be regarded as one of the causes of hyperglycæmia in diabetes mellitus, nowhere in the whole literature of experimental work do we find any intimation that this flooding of the blood with sugar may be due to excessive splitting off of carbohydrate radicals from protein, or to new formation from fat, and thus be a primary and fundamental cause. It would seem that this overproduction of sugar plays but a secondary part in diabetes—that it is the consequence of sugar hunger in the tissues. The cells of the body are constantly in need of carbohydrate when at rest, and still more so when doing work ; they are unable to make use of the sugar, though in hyperglycæmia they are bathed in an abundance of it ; the same chemical stimuli which in health bring about emptying of glycogen depots or lead to new formation of carbohydrate do so still in diabetes ; fresh sugar is constantly being sent along. The

reserves, which a healthy man always keeps up, are drawn upon. In severe diabetes the sugar-supplying organs have to go on producing as much sugar as they would in a healthy man who, after hard work, had exhausted all his stored sugar, and yet went on working. The only difference is that whereas, in the healthy man, the sugar thus supplied could be utilized to satisfy the need for it, in severe diabetes the protoplasm of the cells seems unable to seize it and convert it into useful glycogen ; the sugar is allowed to pass by unused.

In regard to the chemical process by which sugar-production is reflexly evoked, we must here mention the views which von Noorden and Embden (114A) have recently propounded concerning the circulation of carbohydrates. Just as in the liver [Embden and Almagia], so also in the muscles, it is probable that lactic acid is formed from sugar. Part of this lactic acid reaches the blood, in which the percentage of lactic acid is known to rise during muscular exertion. We believe that this lactic acid, formed from sugar in the muscles, becomes built up into sugar again elsewhere in the body. It is known that, after extirpation of the liver, sugar disappears from the blood, whilst lactic acid rapidly increases. It is but one step further to suppose that this is due to the absence of some hepatic or other ferment capable of converting lactic acid into sugar. Perhaps it is the advent of lactic acid to the liver which gives the signal that the tissues need sugar, and causes fresh supplies to be sent to them. Lactic acid is a strong sugar-producer in diabetic patients. The following is an example of this :

A. T., aged twenty-four years, was receiving a fixed diet containing no carbohydrate and very little meat. On certain days 100 grammes of sodium lactate (the lactic acid was obtained by fermentation of milk) were given in eight portions during the twenty-four hours.

Day.	*Sugar. Estimated by*		*Acetone.*	*Nitrogen.*	NH_3.	*Remarks.*
	Polarimeter.	Titration.				
	Gm.	Gm.	Gm.	Gm.	Gm.	
1	20·0	—	—	—	—	—
2	25·6	—	1·6	19·2	1·1	—
3	29·9	—	1·2	20·4	1·7	—
4	24·6	—	0·8	15·6	1·4	—
5	**29·4**	**30·4**	1·6	18·9	1·9	100 grammes Na lactate.
6	**48·0**	**50·0**	1·5	16·0	0·6	100 grammes Na lactate.
7	33·6	36·0	1·4	15·2	1·8	—
8	22·2	25·2	1·9	25·2	2·1	—
9	**53·5**	**58·8**	2·1	19·1	2·3	100 grammes Na lactate.
10	**45·3**	**51·6**	1·4	—	0·7	100 grammes Na lactate.
11	31·8	34·9	1·5	—	1·8	—
12	22·1	29·4	0·6	—	1·4	—

Probably some lactic acid passed into the urine unchanged, but it could not be detected with certainty. Embden and Salomon (114B), working in my laboratory, had previously found increased glycosuria in a dog suffering from pancreatic diabetes when lactic acid was given.

The only primary overproduction we can speak of is in those cases of hyperglycæmia and glycosuria which follow *piqûre*, and result from sudden emptying out of reserve stores of glycogen. We have seen that such phenomena may occur even in true diabetes, leading to a transitory but extreme rise in the glycosuria.

E.—PANCREATIC DIABETES.

Defective action of the pancreas is the only cause of those disturbances in carbohydrate metabolism which occur in diabetes, such as the poorness of the organs in glycogen and the defective katabolism of carbohydrate, that has been proved with any certainty hitherto. De Dominicis of Naples (115) discovered this simultaneously with von Mering and Minkowski (116), but the doctrine of pancreatic diabetes is always associated with the latter names. Minkowski (117), in particular, has gone so fully into all the questions that arose from the original discovery, and has worked out all the points so thoroughly, that hardly anything fresh has been added by other observers.

This is not the place to enter upon the multitudinous literature of experimental pancreatic diabetes. I would refer the reader to Minkowski's monograph, and to his complete list of references to the pathological aspect of the question; also to the references given by Lépine and Sauerbeck (118). I must also mention Pflüger's, Minkowski's, and Zülzer's new contributions (118A). Other important researches that throw light upon certain aspects of metabolism are alluded to in other parts of this chapter.

After complete ablation of the pancreas in a dog severe diabetes sets in, beginning after a few hours and reaching its height in from one to two days. It ends fatally, as a rule, in a few days, and at longest in a week or two. The clinical features and the metabolic changes of the condition, except in a few minor details, are identical with those of diabetes in man. There are polyphagia, polyuria, polydipsia, hyperglycæmia, much glycosuria, even when carbohydrates are withheld, disappearance of glycogen from the tissues, emaciation, loss of power, excretion of large quantities of acetone and allied bodies and of ammonia, ending with coma and death.

The following details must be mentioned :

1. Pancreatic diabetes can be produced not only in the dog and in other mammals, but also in cold-blooded animals and in birds. In the latter[1] there is often hyperglycæmia only, without any sugar being excreted in the urine [Kausch (119)]. In cold-blooded animals there

[1] In cases where birds do not develop glycosuria after ablation of the pancreas, it must be remembered that during carbohydrate katabolism in muscles lactic acid is formed, and is given up to the blood. In mammals this lactic acid is at least partly resynthesized into sugar in the liver, and thus leads to an increase in the hyperglycæmia and glycosuria. In birds there is another and broader path open to this lactic acid : it may become uric acid after combination with ammonia. Carbohydrate in birds may be regarded as one of the producers of uric acid [von Noorden and Embden (118B)]. Extirpation of the pancreas, moreover, leads to increased impermeability of the kidneys to sugar, so that the non-occurrence of glycosuria in birds is easily accounted for by the peculiar metabolic changes in the lactic acid in them.

is no diabetes if the liver is extirpated at the same time as the pancreas [Markuse (120)].

2. After complete ablation of the pancreas, most carbohydrates, certainly glucose, starch, and cane-sugar, are almost entirely recovered in the urine as grape-sugar. A considerable proportion of lævulose becomes katabolized. During starvation, and on meat feeding, 2·8 to 3 parts of sugar appear in the urine for every 1 part of nitrogen. In such cases one speaks of " complete " pancreatic diabetes.

3. If a minimum of one-fifth of the pancreas is left in the dog, diabetes does not supervene. If the remnant is less, an " incomplete " diabetes may ensue, comparable to the milder cases in man. Sandmeyer (121) has shown that this slighter form may progress and become " complete " from gradual degeneration of the residual piece of pancreas.

4. When the animal is in very low condition and marantic, either from starvation or from intercurrent disease, the glycosuria gradually diminishes, even though the pancreas be totally ablated [Minkowski, Thiroloix, Hédon, Lüthje (122)], and though sugar is still met with in the blood. Lüthje found as much as 0·312 per cent. of sugar in the blood in such a case.

5. The fact that the secretion of the pancreas no longer enters the intestine has nothing to do with the origin of the diabetes. This is proved both clinically, in cases where the pancreatic ducts are occluded, and by experimental transplantation of the duct [Minkowski, Hédon, Thiroloix (123)].

The discoverers of pancreatic diabetes came to the conclusion that the normal pancreas secretes " something " internally, which is indispensable for the proper metabolism of sugar. This hypothesis has found support on all sides, and has never been seriously contested. We are not able at the present time to advance the theory of pancreatic diabetes without it.

There have been hosts of experiments made, and many interesting details have come to light, in regard to the remoter consequences of ablation of the pancreas. For instance, Lorand (124) discovered that the thyroid gland begins to secrete colloid in greater abundance. This seems to depend upon some metabolic relation between the two glands, but we can as yet form no clear mental picture of the process. The fact is the more remarkable in that under conditions of hyperactivity of the thyroid gland—for instance, in Graves' disease—alimentary glycosuria is either spontaneous or may be very readily produced (125). Chvostek described this, but I am bound to say that I agree with my pupil, Zülzer, and with Strauss and Naunyn, that it is not of very common occurrence. It appears to be associated with particular phases of the disease. On the other hand, glycosuria often follows administration of thyroid extract [Ewald, von Noorden, and others (128)], more commonly so in spare than in stout individuals.

The theory of the pathogenesis of pancreatic diabetes seemed to enter upon a new and brilliant phase when Lépine (129), after numerous and most laborious investigations, concluded that both after ablation of the pancreas and in spontaneous diabetes in man there was a diminution

in the "*glycolytic ferment*" in the blood. A very active discussion of Lépine's results followed, the verdict being that his methods were not reliable (130). There seems to be no doubt that the blood contains a sugar-destroying ferment. Some maintain that this is identical with the widely distributed oxidizing ferment [Schmiedeberg, Jaquet, Spitzer, Salkowski], whilst others deny this [Jacobi, F. Blumenthal (132)]. No significant difference, however, has been proved to exist between the blood of diabetic and of non-diabetic animals and men. Even in the most recent work upon glycolysis [Stocklasa, Simacek, Sieber, Feinschmidt, Braunstein (133)] there are such objections to the methods meployed that the entire foundation of Lépine's researches seems to have collapsed. There is no recognised test by which to be sure of the presence of a glycolytic ferment. I gave this as my opinion in my textbook upon "The Pathology of Metabolism." There are many *a priori* arguments against Lépine's theory. He devoted his attention to glycolysis in the blood, whilst all the evidence goes to show that the disorders of sugar katabolism are to be sought for in the tissues. Lépine now acknowledges this himself.

Moreover, a calculation made by Kraus (130) shows that the glycolytic power of the blood is unable to cope with more than a small quantity of sugar. Any diminution in this power must have but an insignificant effect, and could have no marked influence upon sugar metabolism.

Again, Cohnheim (134) advances another view. He says that neither pancreatic emulsion nor the juice expressed from muscles can separately exert much glycolytic action, but that when both juices act together upon glucose the latter is broken up with great energy. This would seem to show that the von Mering-Minkowski theory is right—namely, that the pancreas gives back "something" to the blood, and that this "something," when carried to the tissues, renders the katabolism of sugar possible. Rahel Hirsch reported similar researches simultaneously with, and quite independantly of, Cohnheim (135). The latter, in his second publication on the subject, states that this "*activator*" derived from the pancreas is not destroyed by moderate heat. Although Arnheim and Rosenbaum, and Sehrt (136) published confirmatory results soon afterwards, Embden and R. Claus (137) have completely overthrown the whole of Cohnheim's teaching by some extremely careful work they did in my laboratory.

We are therefore in absolute ignorance at present as to how the normal pancreas assists sugar katabolism in the tissues, and how extirpation of the pancreas interferes with the metabolism of sugar. We can only theorize.

This unsatisfactory state of our knowledge of the real nature of pancreatic diabetes is all the more to be deplored in that changes in the pancreas certainly play some considerable part in human diabetes. Some authors even go so far as to believe that in every case of real diabetes—excluding, that is to say, cases of mere transitory hepatogenous glycosuria—the influence of an affected pancreas is at work. Minkowski upheld this view; Naunyn and Hoppe-Seyler (138) inclined towards it; I myself become more and more convinced that it must

be so. Researches in pathological anatomy during the last fifteen years have convincingly shown that the pancreas shows changes of different sorts and of varying degrees in a very large proportion of cases of diabetes. I refer the reader to the summaries of Dieckhoff, Williamson, von Hansemann, and Sauerbeck (139). Much more remarkable than the finding of disease of the pancreas in many cases is the fact that in some patients whose diabetes has been very severe, with all the characters of pancreatic diabetes, the pancreas has shown either very slight macroscopic and microscopic anatomical changes, or even none whatever. I should like to add to the observations mentioned above (139) that I have seen several such cases, in which so illustrious a pathologist as Weigert reported the pancreas to be in every respect normal, notwithstanding the most minute search for evidence of disease. The disorder of function is most commonly observed when the gland is atrophied, when there is sclerosis of its connective tissue, and when there are diffuse endarteritic changes—in other words, when the anatomical changes are such as interfere most thoroughly with the nutrition of the glands. Since, on the other hand, there are cases in which, notwithstanding severe changes in the pancreas —for example, carcinoma—there has been no diabetes, we are compelled to assume :

1. That the influence of the pancreas upon carbohydrate metabolism is a specific function of the gland, interference with which our present pathological methods are not always able to demonstrate.

2. That the influence of the pancreas upon carbohydrate metabolism may remain normal when only a small portion of the gland remains intact, provided that this residual gland tissue has preserved the specific function we are here speaking of.

There need be no change in the above generalizations, even should pathologists succeed in establishing as a fact that which Opie and Ssobolew (139A) propounded independently as a theory—namely, that the influence of the gland upon carbohydrate metabolism is dependent not upon the entire organ, but only on the so-called islands of Langerhans. These, according to a recent view, are blood vascular glands, encapsuled in the pancreatic tissue, and concerned in internal secretion.[1] The question is *sub judice*. Sauerbeck supports it strongly, but several writers [Karakascheff, Herxheimer, Reitmann, Gutmann (140)] subject it to criticism. The matter is of so anatomical and embryological a nature that it is impossible to go more fully into it here.

Minkowski has discussed at length the idea that perhaps some other organ besides the pancreas may have a metastatic action upon carbohydrate metabolism. His own careful experimental work, and his criticism of the results, led him to negative this idea ; but at the present day it is not possible to answer the question definitely.

The action of secretin upon the activity of the external and internal pancreatic secretion in diabetes has been investigated by Moore, Edie and Abram (140A). Spriggs, at an earlier date, had made injections of secretin solutions in a case of diabetes, but with negative results. In three

[1] Rennie and Fraser (*B. J.*, 1907) administered "islets" from *Lophius piscatorius*, and obtained slight, but limited reduction of the glycosuria in diabetics.

young diabetics Moore, Edie and Abram obtained remarkable decreases in the sugar excretion after the administration of secretin. They suggest that if a causal connection exists in these cases, it is probable that the glycosuria results from a failure of the chemical excitant—secretin—in the duodenum, and that this in the end might lead to permanent abolition of the internal secretion of the pancreas. Bainbridge, Beddard, and Charles report negative results. (*B.J.*, 1906, and *B M.C.J.*, 1906).

F.—SUPRARENAL DIABETES.

F. Blum (141) observed that an intravascular injection of suprarenal extract evoked glycosuria to a very slight extent. This glycosuria was temporary, but it sometimes lasted for a day or two. Herter and Richards, Herter and Wakeman, Vosbourgh and Aronsohn (142) showed that the substance which evoked glycosuria was identical with adrenalin, which had in the meanwhile been obtained from the suprarenal bodies. The sugar in the blood is increased in those cases of glycosuria which have resulted from the therapeutic use of adrenalin injections in man (143). I have seen such a case.[1] In diabetic patients adrenalin increases the glycosuria [Noel Paton].

Herter and Vosburgh and Richards group adrenalin glycosuria with those hepatogenous forms which are due to direct chemical stimulation of the liver cells. They found that the blood as it left the liver was richer in sugar than normal.

Piperidin-poisoning in animals produces a sugar excretion which in many points is similar to that due to adrenalin. Underhill (142A) holds that it is due to paresis of the respiratory centre and deficient oxygen supply to the tissues, corresponding to the glycosuria caused by dyspnœa which Araki described.

There is a certain degree of antagonism between the pancreas and the suprarenal bodies. In the case of the pancreas it is the suppression of a function which disturbs sugar metabolism; with the suprarenals it is increased output of some substance (? increased function) which evokes glycosuria. The latter was well shown by an experiment of Herter's. In animals it was found unnecessary to greatly injure the suprarenal bodies; mere pressure of them between the fingers was sufficient to cause glycosuria at once. Another observation of this same worker also seems to demonstrate the antagonism between the two glands.

[1] Adrenalin injections were made in the case of a male patient M., on account of chronic œdema of the left leg resulting from the prolonged use of a plaster splint. Injections of 0·5 to 2·0 milligrammes were commenced on November 12, 1903, and continued daily until January 5, 1904. On November 15 there were already traces of sugar; up to December 15 sugar only appeared occasionally, and remained small in amount; it was too little to estimate. From this date the glycosuria persisted from day to day, and rose (when 1·5 to 2·0 milligrammes of adrenalin were given) gradually up to 1·0 and 2·0 per cent. The sugar reaction began about one and a half hours after the injection of adrenalin, and disappeared again about two to four hours later. Simultaneously with the injections the patient was then given 100 grammes of cane-sugar dissolved in 300 c.c. of water; the sugar rose to 4·1 per cent., but entirely disappeared within two to four hours. After the adrenalin treatment was discontinued, it was impossible to produce glycosuria in this patient, even when he was given maximal quantities of bread and sugar.

When an animal has its suprarenal bodies removed as well as its pancreas, the glycosuria is not so marked as it is when the pancreas alone is ablated. The experiment, of course, is by no means sufficient by itself to prove that the two viscera act in constant physiological opposition.

In the case of adrenalin we obviously have to do with a toxic glycosuria. Herter believes the toxic effect may be upon the pancreas. We do not know at all what influence, if any, the suprarenal bodies have in human diabetes. Blum and others presume that the suprarenal bodies are affected in so-called "bronzed" diabetes, but in making this hypothesis they depart entirely from actual fact. Between the bronzing of Addison's disease due to disorder of the adrenal capsules and the clinical phenomena of bronzed diabetes the only connection is one of name. The suprarenal bodies are not necessarily diseased in bronzed diabetes, which is a particular complication of diabetes with hæmatolysis, cirrhosis of the liver, enlargement of the spleen, and accumulation of a hæmatogenous pigment containing iron.

It is worthy of note that Blum maintains that in some of his experiments he has "clearly demonstrated the conversion of fat into carbohydrate." I myself, though perhaps I hold more strongly than anybody else the view that fat can produce sugar, am unable to find any proof of this kind in Blum's work. His conclusions go to pieces under E. Pflüger's stern criticism.

Aronsohn contends that adrenalin glycosuria depends upon the pyrexia produced. This is disputed by Ellinger and Seelig. The glycosuria which results from adrenalin injection during fever only varies with the amount of pyrexia when the kidney functions are damaged at the same time—for instance, in the death agony of the animals experimented upon. Kidney affections alone, without fever and infection, bring about the same result (142B).

G.—ACROMEGALY DIABETES.

The clinical picture of acromegaly has become more and more clear of late years, and it is remarkable how often it is associated with diabetes mellitus as a complication. An interdependence between the two conditions cannot be doubted. Loeb (144) was the first to show that tumours of the pituitary body are often associated with melituria (*cf.* 145 also).

From my own experience I may mention that of the five cases of acromegaly that I have seen of recent years, four had diabetes. The latter began long after the acromegalic changes. In two cases the diabetes was in no way distinguishable from the ordinary form. In the other two patients the glycosuria varied from time to time quite independently of the diet; other and unknown factors, perhaps neurogenous, seemed to be at work here.

Writers upon acromegaly diabetes take the most various views. Some maintain that two entirely separate diseases are present together. This may be true in certain instances, but the frequency of the association argues strongly against so superficial a diagnosis. Others lay stress upon

the pressure exerted by the pituitary tumour on the brain, and think that the fourth ventricle and its surroundings are thus affected, causing a chronic neurogenous glycosuria. Others, again, particularly Lorand, believe there is direct inter-relationship, by internal secretion, between the blood vascular glands of the hypophysis cerebri and the pancreas. They think that disturbance in the internal secretion of the pituitary body (? hyper- or hyposecretion) diminishes the internal secretion of the pancreas.

We thus have before us a series of hypotheses which are still *sub judice*. We do not know the facts sufficiently well to discuss any of them more fully just now.

II.—ENERGY EXCHANGE.

Pettenkofer and C. Voit (146), in a research carried on for a week with their large respiratory apparatus, determined the oxygen absorption and carbon dioxide excretion of a patient suffering from severe diabetes. For each kilogramme of body-weight 34 calories were used up. The oxygen absorption, the carbon dioxide excretion, and the heat-production were, weight for weight, the same as in health. The authors did not make their results clear in their first publication, and the idea got abroad that there was an enormous reduction in the oxidation processes of diabetic patients. Livierato (147) said his own experiments showed this, but his methods were open to criticism. More recently a research exactly similar to that of Voit and Pettenkofer was carried out by Lehmann and Ebstein (148) upon a diabetic patient.[1] There was a daily output of 11·02 grammes CO_2 per kilogramme body-weight; Voit's figure was 11·5 grammes, so that the agreement is remarkably close. We cannot here go into the oxygen estimations made by Robin and Binet (149), against which a whole series of objections arise.[2]

Observations of much greater importance have been made upon the amount of oxidation in diabetic patients by means of the Zuntz-Geppert respiration apparatus. The technique and reliability of these estimations have been discussed in the physiological portion of this work. The experiments of Weintraud and Laves (151) have often been quoted, but they must now be put upon one side because they were made upon patients who were neither fasting nor at complete rest. The determinations of the respiratory exchange which were made by Leo, Stüve, Nehring and Schmoll, and Magnus-Levy (152) are free from all objections, and gave the following figures for the oxygen used up in the fasting state (see table, p. 567).

Except in Leo's third and Magnus-Levy's fourth cases the oxygen used in all the patients was normal, or at least not diminished. The

[1] Curiously enough, Ebstein, captivated by his theory, gives a different interpretation to this research. In various places in his writings (150) he maintains that his work proves diminished oxidation and CO_2 production. The daily production of CO_2 was 687·8 grammes. This is only small when compared to the CO_2 production of a man in full activity. Ebstein has overlooked the fact that in proportion to his patient's body-weight (62·5 kilogrammes) this figure is perfectly normal.

[2] See Magnus-Levy (152) for a full criticism.

glycosuria was slight in some cases, severe in others. The two exceptional patients were obese, and this fully accounts for the low O_2 figures per kilogramme body-weight (see Obesity).

Case.	*Oxygen. Per Kilogramme and Minute.*	*Author.*	*Remarks.*
	c.c.		
1	4·01	H. Leo	—
2	3·87	,,	—
3	2·84	,,	—
4	3·47	,,	—
5	4·26	,,	—
6	4·04	R. Stüve	—
S.	4·47	Nelving and Schmoll	—
W.	3·70	,, ,,	—
1	4·67	A. Magnus-Levy	Thin.
2	5·17	,, ,,	Only 33·8 kilogrammes.
4	2·82	,, ,,	Obese.
5	3·88	,, ,,	—

Kaufmann's (153) observations upon the O_2 requirements of a normal dog and of one suffering from pancreatic diabetes are in agreement with the above. He found no difference between the two. Weintraud and Laves (154) had previously observed the same—the oxygen used per kilogramme body-weight per minute was 13·35 c.c. before ablation of the pancreas, 13·41 c.c. afterwards.

In opposition to the facts thus learned from the gaseous exchange, many physicians maintain that the actual food requirements of patients suffering from severe diabetes are less than those of healthy individuals. This must imply a need for less calories than usual. I have only seen this actually demonstrated in one case. This was a patient of Weintraud's (155). In an observation extending over sixty-seven days the body-weight increased 6·5 kilogrammes, although the food yielded but 25 calories per kilogramme. Weintraud himself is very far from generalizing upon this one experiment. The patient was very ill; his weight to start with was only 49 kilogrammes. We have already seen that in some patients, even when there is no diabetes, the calories actually required are occasionally very low indeed. The above seems to have been one of these exceptional cases. When his nutrition had improved he began to require the normal number of calories.[1]

When Kolisch and Schlesinger (156) begin to apply the above experience to cases in general, it is necessary to criticise their results. Kolisch gives no figures. Schlesinger's calculations are open to objection throughout. The same individual may exhibit such tremendous differences in calorie production—for example, 10·2 calories per kilogramme one day and 49 the next—that wide generalizations cannot be made. It is held by von Noorden, Lusk, Voit, Naunyn, Hirschfeld, Magnus-Levy, and others that the calorie requirements of a diabetic patient are at least equal to those of a healthy man, and may even be greater

[1] See Magnus-Levy (152) for a full account of the case.

if the sugar lost in the urine is taken into account (see below). I have already opposed Kolisch in this discussion (158), and I must here repeat that permanent increase in the weight of diabetic patients can only take place when at least as many serviceable calories are supplied to them as healthy people require under similar external conditions. I have, without the least exaggeration, had experience of this more than one thousand times.

We must repeat that, even though there are a few isolated exceptions, both respiration analyses and general clinical experience teach that the energy used up by a diabetic patient is not less than that used up by a sound man. This being granted, the food requirements can easily be calculated. Perhaps an example may be useful :

Ernst F., aged forty-six ; weight 65 kilogrammes ; well nourished. His occupation was light. His food requirements would at least be $65 \times 35 = 2{,}275$ calories. For six days consecutively he received per diem :

Protein	102 grammes	=	418 calories
Fat	206 ,,	=	1,916 ,,
Carbohydrate	80 ,,	=	328 ,,
			2,662 ,,

He excreted upon the average per diem :

Glucose	170 grammes	=	636 calories
Oxybutyric acid and acetone	26 ,,	=	118 ,,
			754 ,,

He was thus losing in his urine 754 calories, which would have been utilized by a non-diabetic subject. The above diet therefore supplied him with only 1,908 calories that he could use—probably even less, because the acetone expired from the lungs was not measured, and therefore was not taken into account. His daily requirement was calculated to be 2,275 calories ; there was, therefore, a daily deficit of $2{,}275 - 1908 = 367$ calories.

The man's body had to supply 367 calories from its own tissues. If this be reckoned as fat, he must lose 40 grammes of fat daily. If the same diet were continued under the same conditions, the patient must necessarily waste away until his nutrition fell to that point at which the diet in question would be sufficient to maintain it.

We thus see that a diabetic patient, if he is not to lose weight, must either take a mixed diet whose energy exceeds that required for a healthy man by the amount that drains away as sugar and acetone bodies, or else he must so arrange the food which is to supply his energy that the loss of sugar may be reduced to a minimum. In consequence the diet must consist mainly of protein and fats.

We now understand that remarkable desire for food, the polyphagia, of diabetic patients. They eat voluminously, including much carbohydrate, unless their diet is regulated by the physician. The hunger of the stomach becomes satisfied for the moment, but soon returns because the hunger of the tissues is not alleviated. This tremendous appetite of the diabetic disappears at once when the useless sugar is limited and replaced by proper quantities of protein and fat. With the cessation of the polyphagia the emaciation stops too.

For the peculiarities of the respiratory quotient in diabetes, see Vol. I.

III.—PROTEIN METABOLISM.

It has long been known that protein metabolism may reach unusual heights in diabetes. It is not at all uncommon to find 30 to 40 grammes of nitrogen in the urine. This was even more the case formerly when diabetic patients were given large quantites of protein than is now the general custom, thanks to the warnings of Kolisch, Lenné, Naunyn, von Noorden, and others (159). In different individuals the large quantities of nitrogen excreted may have very different origins.

1. The nitrogen elimination may be high because the diabetic eats much more proteid than does a healthy man. If, for example, his diet contains 200 grammes of protein and more, as it does on the Catani system, some 32 grammes nitrogen will be accounted for in the urine.

2. The diabetic patient excretes more nitrogen than does a healthy man upon the same diet. There may be two causes for this :

(*a*) *Loss of Nitrogen from Underfeeding.*—The katabolism of protein is greater than in health, because a normal man saves his protein by burning up carbohydrate ; the diabetic excretes a great part of the circulating carbohydrate without utilizing the potential energy in it. Von Voit has pointed this out very clearly (160). The conditions under which the diabetic lives may be imitated to some extent in health by decreasing the carbohydrate in a sound man's diet by the amount that the diabetic passes in his urine. Lusk (161) succeeded in showing that under these circumstances the protein katabolism of a healthy man is no less than that of a diabetic. The same was shown by some experiments carried out by Miura and Kayser (162) under von Noorden's direction, and also by some work of Hirschfeld's (163). This increase in protein katabolism, depending as it does upon deficiency of carbohydrate and consequent underfeeding, can scarcely be termed pathological. It is true that it is a phenomenon closely dependent upon the fundamental cause of the diabetes, but still it is only a result of the physiological relations that always subsist between carbohydrate and protein katabolism.

It now seems probable, as I hinted in my text-book (p. 389), that in every case of diabetes in which more nitrogen is found in the urine than in the food, and in which the nitrogen output is larger than that of healthy controls, the whole fault is one of underfeeding. The following experiment may serve as an example : The patient took food equivalent to 2,662 calories of energy ; on this amount a healthy man would have undoubtedly maintained himself in nitrogenous equilibrium, or, indeed, might have actually stored up nitrogen. For the diabetic, however, there was a daily deficiency of 367 calories, and there was complete absence of that sparing of protein which carbohydrate, as a rule, exerts. The man could only utilize some 29 calories per kilogramme. The nitrogen balance was as follows :

Intake in six days	97·8 grammes of nitrogen.	
Output in urine in six days	102·8	„ „
Output in fæces in six days	6·8	„ „
	– 11·8 grammes nitrogen deficit.	

or about 2 grammes of nitrogen per diem. The case was one of considerable underfeeding. The loss of nitrogen was not to be wondered at (see also reference 164).

These experiences are confirmed the opposite way round. It is not difficult, as metabolism researches have shown, to maintain or raise the nitrogen level of a diabetic so long as the patient receives a diet containing enough, or more than enough, calories for his daily needs [von Mering, von Noorden, Weintraud, Lüthje, and others (165)]. It is possible for diabetics to store up nitrogen when they are placed under suitable dietetic conditions, with limitation of the carbohydrate, even when their supply of energy in calories is less than the average in health [Ajello and Cacace (164)]. I have shown that a diabetic may maintain his nitrogenous equilibrium over a long period upon amounts of protein that are far lower than the normal average, provided the total calorie supply is adequate. For example, a diabetic patient weighing 70 kilogrammes, and suffering from a mild form of the disease, remained in nitrogenous equilibrium for three weeks upon 60 grammes of protein per diem, with 250 grammes of fat, and the amount of carbohydrate that small quantities of green vegetables contained. The food was all weighed, and the urine and fæces analyzed. Lüthje (95) has shown that almost colossal quantities of nitrogen may be retained by diabetic patients. In one case under his care 395 grammes of nitrogen were stored up within five weeks. I can confirm this. For example, I have seen a diabetic, who had sunk very low, retain 124 grammes of nitrogen in eighteen days. There was no nephritis. The man took 110 to 115 grammes of protein per diem, and the calories utilized, after deduction of those lost as glucose and acetone bodies, amounted to 45 to 50 per kilogramme.

(*b*) *Loss of Nitrogen from Toxogenous Protein Katabolism.*—Perhaps there are other forces at work in the body attacking cell protoplasm in a specific way. We spoke of the loss of nitrogen which directly resulted from the glycosuria, as physiological. The processes of protein destruction now under discussion would be pathological. They would be comparable to the toxic protein katabolism that occurs in fever, in phosphorous-poisoning, in leuchæmia, etc. It is only necessary to prove that a diabetic patient loses nitrogen in spite of his food, after deduction of all loss, being sufficient in amount to maintain nitrogen metabolism in health. Von Mering (165) has observed such a condition of affairs several times in advanced cases, particularly in that stage at which copious excretion of oxybutyric acid in the urine occurs, or at which diabetic coma is imminent. This coma affords a clear picture of a severe intoxication. It is easy to understand that poisons which ultimately lead to fatal paralysis of the central nervous system may, at an earlier stage, cause much disorder of the body cells.

Later investigations have not succeeded in proving that any toxic protein katabolism occurs in coma [Magnus-Levy, Lüthje (166)]. One

case which Münzer and Strasser (167) described as such is inconclusive, because there was a pulmonary abscess with pyrexia at the same time, and this alone may have accounted for the toxic destruction of protein. I think no great stress should be laid upon negative cases. It may be that immediately before death retention of nitrogen occurs and obscures any increase in protein katabolism.

On the other hand, there are many observations in which, without coma, the nitrogen balance was such that there was at least a possibility of toxic protein katabolism [Wegeli, Hesse (168)]. My own opinion is that most of the metabolism researches in diabetes that have been published afford no data for deciding the question. Amongst other things, they do not fully comply with the stringent conditions that such experiments, to be decisive, require. In cases where the arrangements were free from objection no toxic destruction of protein could be actually demonstrated (see above), and yet it undoubtedly seems to occur clinically. We often see diabetics, who for years and even decades have maintained their powers well, ultimately break down in spite of full supplies of nourishment ; sometimes the omentum may remain loaded with fat, whilst the muscles all over the body dwindle away. There seems to be something which destroys the protoplasm of the muscles and energetically opposes its being built up afresh, in spite of an abundant supply of protein and calories in the food. I have often been able to show that in such cases 100 grammes of nitrogen or more, corresponding to 3 kilogrammes of meat, were retained in the body, and yet the muscles remained just as flabby as before. After glancing at these clinical facts, which should point the way for future investigations, it can only be said that in diabetic patients no pathological loss of nitrogen has been demonstrated; that it is relatively easy in them to bring about storage of nitrogen; that toxic destruction of protoplasm is not thereby excluded; and that in diabetics, even more so than in healthy people, it is doubtful whether retention of nitrogen really means a storing up of protein or a laying on of muscle. Lately, but not in a diabetic, Dengler and Mayer (168A) determined the gaseous exchanges in a patient who was thus being fattened up, and obtained important biological proof that the nitrogenous substance which was stored in such abundance had nothing to do with increasing true flesh and protoplasm (see Vol. I., Overfeeding). Lüthje (95) expresses the same view; he was led to this belief by the rapidity with which the retained nitrogen could disappear again.

A few further facts, such as increased excretion of purin bodies, discussed below, seem to indicate that a great destruction of nuclei can take place in severe cases of diabetes.

IV.—THE CARBOHYDRATES OF DIABETIC URINE.

The sugar which comes to one's mind when diabetes mellitus is spoken of is dextrose. It has only been recently pointed out that other varieties of sugar may be present in human urine—spontaneous lactosuria,

lævulosuria, pentosuria. The first of these is discussed in the physiological portion of this work; the two others have a chapter to themselves, since, unlike lactosuria, they are really pathological anomalies of metabolism, and yet are quite distinct from diabetes mellitus. This is true of pentosuria, at any rate; lævulosuria is not altogether an entity by itself.

During the last few years it has been shown that, even in diabetes, dextrose does not hold the wholly exclusive position it was formerly believed to. Sometimes spontaneously, sometimes as the result of special conditions of the food taken, other sorts of sugar besides dextrose may appear in diabetic urine.

A.—DIFFERENT CARBOHYDRATES.

1. Lævulose.

We are not here discussing cases of pure lævulosuria such as were first described by Seegen and Külz (169). Lævulosuria as an accompaniment of diabetic glycosuria, and independent of the eating of fruit-sugar (*cf.* Vol. I.), had very seldom been recorded (170), until Rosin and Laband (175) showed, by careful and incontrovertible observations, that it is comparatively common. Sometimes lævulose occurred in traces just demonstrable by the Seliwanoff test; sometimes it amounted to 0·3 to 1·2 per cent., or about one-fifth to one-fourth of all the sugar in the urine. This was confirmed by Lion, Schwarz, Umber, and Graul (172). My own observations in something like one hundred cases of diabetes lead me to a similar conclusion, except that I would say that an obvious lævulose reaction is extremely rare in the slighter cases of the disease. In severe cases the Seliwanoff test, if done with care, usually gives a marked positive reaction. When the glycosuria diminishes under treatment, the lævulose becomes less and less, disappearing altogether as the glycosuria approaches zero. I think figures as high as some of those of Rosin, Laband, and Umber are exceptional.

When lævulose occurs in the urine, one would expect to find it in the blood too. Rosin detected it here, and we know from the work of Pickardt in my own ward, and from that of Strauss and Neuberg[1] (173), that lævulose is not an ordinary constituent of the normal juices. Probably Schlesinger is right in saying that the transformation of dextrose into lævulose may sometimes occur in health to a slight extent, for this may happen very readily *in vitro* in the presence of an alkali [Lobry de Bruyn and von Ekenstein (174)]. If this be so, the appearance of lævulose in diabetic urine would be no new departure in the patient's metabolism, but would indicate an increase in his glycosuric tendency.

The condition must be termed *spontaneous* lævulosuria, because it occurs independently of the giving of lævulose. In my cases, at least, the food contained no lævulose at all. In addition to this form, however, there is another which we may term *alimentary* lævulosuria.

[1] The work done by Neuberg and Strauss has recently been attacked by R. Ofner. For the methods of detecting lævulose in human tissue fluids, see *Zt. Physiolog. Chemie*, xlv., 359, 1905.

Külz was the first to show that diabetic patients, as a rule, deal with lævulose and its polysaccharide inulin better than they do with starch, cane-sugar, or grape-sugar. For instance, the urine may remain free from sugar when 50 grammes of lævulose are eaten, although a like amount of starch or cane-sugar given to the same patient would lead to 6 or 10 grammes or more of sugar being excreted. This discovery of Külz's has in the main been confirmed by all writers (176). The distinction is not permanent, however. If the lævulose be given continuously, in about three to five days it is found that the sugar excreted becomes no less than it is when other carbohydrates are given to the same patient [Socin, Naunyn, Bohland, Palma, and von Noorden (176)]. The excreted sugar is mostly dextrose. Probably this is derived from the hepatic glycogen formed from the lævulose. In addition, however, there is often some lævulose as well—alimentary lævulosuria. Its amount is seldom more than one-tenth to one-eighth that of the dextrose. My own observations lead me to think that when lævulose first causes glycosuria, dextrose alone appears; only after some time, or after giving lævulose in large quantities by the mouth, is the amount of lævulose in the urine sufficient to estimate. This agrees with our previous conclusion—namely, that lævulosuria is the result of a more advanced metabolic disturbance than is simple glycosuria.[1]

2. Cane-Sugar.

Cane-sugar is not found in diabetic urine. It is not known whether or not it might appear if very large amounts of it were eaten. To argue *a priori* from its composition—namely, dextrose plus lævulose—it should have a feebler action upon glycosuria than have starch and dextrose [Külz (63)]. It should thus occupy a position midway between dextrose and lævulose. This is not borne out by practical experience. Külz seems to have underestimated the detrimental action of cane-sugar [von Noorden, Naunyn (177)]. I may cite an interesting observation upon the effects of cane-sugar as compared with the effects of the same amount of its two components:

The patient was suffering from a mild degree of glycosuria. Upon strict diet sugar was absent from the urine. The different kinds of sugar were added to an otherwise "strict diet" to the extent of 100 grammes on two consecutive days one half at 8 a.m., the other half at 10 a.m. Between each period of two days one day of ordinary strict diet was interpolated. The total sugar in the urine for the three days—two with added sugar and one with strict diet—was estimated, and thus corresponded with the giving of 200 grammes of one sort of sugar or another.

Carbohydrate (for every Two Days).	*Sugar in Urine.* Gm.
200 grammes glucose	38
200 ,, lævulose	—
200 ,, starch	36
200 ,, cane-sugar	34
100 ,, lævulose + 100 grammes glucose	17
200 ,, lactose	26

[1] For the theoretical importance of this behaviour of lævulose, see Vol. I.

These favourable results of giving lævulose are striking, whilst the effects of cane-sugar were worse than those of an equal quantity of dextrose and lævulose together.

Quite recently we have been told by Teschenmacher and von Oefele of diabetic patients who have shown an extraordinary tolerance for cane-sugar (178).

3. Maltose.

Spontaneous maltosuria was described by le Nobel and van Ackeren (179) in one case of pancreatic diabetes with steatorrhœa. It was at first hoped that the appearance of maltose might afford sure evidence of severe affection of the pancreas, but unfortunately this hope has not been realized.

I searched in vain for maltose by van Ackeren's method in three cases of diabetes in which the pancreas was afterwards proved to be grossly diseased.

Lépine and Kottmann (180) have recently reported several cases of spontaneous maltosuria in diabetes mellitus concomitantly with glycosuria, but the conditions which led to this were not clear. They also found small quantities of maltose along with abundance of dextrose in the urine of dogs rendered diabetic by extirpation of the pancreas. This is contrary to Minkowski's results. He failed to find maltosuria in pancreatic diabetes, even when the salivary glands were extirpated as well as the pancreas. We ourselves have found maltose under these conditions, but only quite exceptionally. It may be remarked in passing that normal urine may contain traces of isomaltose [Baisch, Lemaire, Pavy and Siau (181)].

When maltose is administered by the mouth in cases of diabetes it is excreted as dextrose. The amount thus eliminated varies with the degree to which the patient can still katabolize dextrose. The maltose itself does not pass straight out into the urine [P. Palma (176)].

There are certain individuals who have very little tolerance for maltose, although they may be able to deal with other forms of sugar quite well, or at least relatively better. Beer is our only food-stuff which contains much maltose. I have often seen patients who come for advice because sugar has been discovered in their urine. The history is that they had been drinking beer freely before the discovery. Further observations prove in these cases that the mellituria only occurs after beer-drinking, whilst cane-sugar and any quantity of starch cause no glycosuria. In one patient ½ litre of beer was enough to produce mellituria, in others much more. It seems that in these people the maltose is not properly dealt with, either in the bowel or in the circulation. One must be on the look out for such peculiarities, lest one diagnose a harmless idiosyncrasy as a dangerous disease. Unfortunately, no steps were taken to determine whether the sugar in these cases was glucose, or, as I think more probable, unaltered maltose.

4. Lactose.

Spontaneous lactosuria only occurs towards the end of pregnancy and during lactation (see Vol. I.). I have three times observed a marked degree of lactosuria in diabetic women who had lately been confined.

All observers are agreed that diabetic patients do much better upon lactose than they do upon dextrose (182). This is borne out by the remarkable tolerance for milk exhibited by many of the patients. It is a fact of great therapeutic importance ; but, just as in the case of lævulose, the tolerance is not always lasting. It disappears when the milk diet is long continued, so that the milk cure recently advocated by Winternitz and Strasser (183) is, unfortunately, not of universal application [von Noorden, Naunyn (177)].

Nevertheless, I agree with Winternitz that there are patients who do very much better upon an exclusively milk diet, gradually increased, than they do upon a mixed diet. It is very important not to be dogmatic ; each case of diabetes must receive individual investigation, and each case requires its own line of treatment. In this respect I would refer to the similarity between this milk cure and the oat cure I myself have recommended.

The sugar which appears in the urine after the administration of lactose is dextrose ; the same is true after giving galactose [Voit (184)]. If the lactose is taken in very large quantities, a small portion of it passes into the urine. De Jong mentions this, and I have seen it three times after taking 100 grammes of pure lactose, and twice in diabetic patients with marked glycosuria who were upon an exclusively milk diet of from $2\frac{1}{2}$ to 3 litres per diem.

Alimentary lactosuria may occur in children who have no diabetes (see chapter upon Metabolism in Childhood). Many cases of glycosuria have been described in infants with disturbance of the gastro-intestinal functions. Grosz showed that this sugar was dextro-rotatory, and would not ferment. He concluded it was lactose, or a product of lactose. Langstein and Steinitz (184A) identified lactose and galactose in the urine of infants who had gastro-intestinal mischief, but who were taking the breast, and this although lactase was found in the stools. In my own wards my former assistant, Zülzer, investigated the matter ten years ago, and found that infants under a year old, even without gastro-intestinal disturbance, might excrete considerable quantities of lactose in their urine, if to the ordinary diet of milk and oat-water about 30 grammes of lactose were added per diem. We have had an opportunity of pursuing this investigation further, and have been able to identify the sugar as lactose ; it reduces, is dextro-rotatory, does not ferment with *Saccharomyces apiculatus*, and the osazone is soluble in hot water. The urine often contained 1 and 2 per cent. of this substance.

5. Glycogen.

Concerning glycogen in diabetic urine, see Hyperglycæmia.

6. Pentoses.

Pentosuria is fully discussed in another part of this book. In a very important piece of work upon pentosuria Külz and Vogel state that they frequently find small quantities of pentose along with the dextrose in diabetic urine. They also met with it in dogs after ablation of the pancreas, but only after the animals had had nothing to eat for some time. Von Alfthan (186), who has done most brilliant work upon the urinary carbohydrates, regards pentoses as constantly present in diabetic urine. This seems to me to be going too far. It is certain that Bial's test, which is extremely delicate, almost always fails in slight, and very often in severe, cases.

The discussion as to the origin of the urinary pentoses and arabinose in diabetes must be left until the origin of pentoses in cases of simple pentosuria is known. For a long while they were thought to be derived from nucleo-proteids, which are known to yield *l*-xylose. Neuberg and Salkowski (187) have recently shown how pentoses may arise from hexoses via glycuronic acid.[1] This is a most important and interesting point in its bearing upon diabetes. Embden, Salomon, and Schmidt, working in my laboratory, have shown it to be more than probable that during the katabolism of *a*-amido acids, and perhaps also of *a*-oxy acids, in the freshly-excised liver, a carboxyl group may be split off, leading to the formation of bodies containing one less carbon atom. If this be so, it would be likely that pentoses should arise from amino-hexoses, or from glyconic acid, which is a probable intermediate substance derived from grape-sugar. Ruff succeeded in preparing arabinose from glyconic acid *in vitro* (187A).

Pentoses given as food seem to behave in diabetic patients just as they do in health. They form little or no glycogen [Cremer, Frentzel (188)], but they are utilized in some way or other ; only part of the pentose, arabinose, rhamnose, or xylose given by the mouth can be recovered from the urine. The amount eliminated unchanged varies enormously, even in the absence of diabetes ; no law controlling this has yet been discovered. For example, there were recovered from the urine and fæces together :

	Per Cent.	
Of rhamnose	about 8	[Lindemann and May (189)].
Of rhamnose	5·15–63·6	[von Jaksch (190)].
Of arabinose	1·0–43·1	,,
Of xylose	18·7–54·8	,,

Salkowski (191) thinks this disappearance of pentoses in the body may depend upon fermentative and bacterial changes undergone before they are absorbed ; but the disappearance occurs just the same when subcutaneous injections are given, whether of arabinose, xylose, or rhamnose, in man [Voit (192)]. Cremer has advanced most important proof of their actual oxidation, by respiration experiments and gas analyses in rabbits.

In their experiments upon the amount utilized in diabetes, Lindemann

[1] See C. Neuberg's contribution to this volume.

and May found the results less favourable than in health ; 16 per cent. of the rhamnose reappeared in the urine and fæces. This, however, may be accidental, seeing how wide the variations may be in the same person at different times. Von Jaksch obtained the following figures :

	Per Cent.		Per Cent.	
Of arabinose (Case 1)	48·9 ;	thereof	11·9	in fæces.
,, (Case 2)	51·0 ;	,,	23·0	,,
,, (Case 3)	82·0 ;	,,	—	,,
Of xylose	0–4			
Of rhamnose (Case 1)	27·6 ;	,,	3·7	,,
,, (Case 2)	33·2 ;	,,	3·6	,,
,, (Case 3)	49·3 ;	,,	21·4	,,

The hope that pentoses might prove to be a suitable food for diabetic patients has not been fulfilled. Great increase in the glycosuria was observed by Lindemann and May, and in one diabetic patient, whose glycosuria had ceased under treatment, the administration of pentose caused the immediate recurrence of dextrose in the urine, persisting for several days. Bergell (194) confirms this. Von Jaksch (193) has also observed other ill-effects, such as diarrhœa and increased, perhaps toxic, destruction of protein.

7. Dextrin and Allied Substances.

Alfthan (195), using the benzoyl-ester method, found about 0·15 gramme of dextrin daily in normal urine (195). He, and Rosin and Laband (171) before him, demonstrated a considerable increase in the amount of dextrin substances in some diabetic urines. Dengler and von Noorden instituted some systematic researches upon this point. The experiments remained unfinished, and I gave the figures we had obtained to von Alfthan, who incorporated them in his elaborate work upon the dextrin substances in diabetic urines (186). In eleven consecutive cases the increase in urinary dextrin was obvious, though the differences between individual cases were great. The amount varied directly with the severity of the diabetes. In one case of Dengler's, where coma ensued a few days after the observations were made, the daily quantity of esters rose from 3 to 4 grammes to 17 to 27 grammes within twelve days, during which time the patient's general condition grew steadily worse. It is impossible to explain the reasons for this yet. We can only record the facts.

8. Glycuronic Acid.

Glycuronic acid is an intermediate product of metabolism. It seems likely that it is derived from carbohydrate. Thierfelder and Loewi (196), however, think it may come from protein. When quantities of aromatic bodies find their way into the circulation, a portion of them enter into combination with glycuronic acid. Whether this combination with glycuronic acid takes place directly, or whether phenol-sugar, etc., have to be formed first [Fischer and Piloty (197)], will not be discussed here. It seems at least certain that the combination occurs in the liver [Embden

(198)]. There is no foundation for Neuberg's (199) criticism of this. Embden was able to confirm his earlier results by fresh experiments that were free from all objections. The fact that some of the substances combine with sulphuric acid, some with glycuronic acid, seems to depend upon a mass action rather than upon the intrinsic nature of the combining bodies. Usually the sulphuric acid preponderates, but there is always a small amount of combined glycuronic acid in the urine also [Mayer and Neuberg]. All these questions have been fully discussed elsewhere (see C. Neuberg's article in this volume).

Hitherto the amount of glycuronic acid excreted has been regarded as depending upon the amount of aromatic substances ready to combine with it. Mayer has recently propounded a converse view that in some cases the oxidation of glucose can be carried as far as glycuronic acid, but no further. He thinks this may occur not only in diabetes mellitus, but also in various severe disturbances of the circulatory and respiratory organs. The excess of glycuronic acid would here be primary, its combination with aromatic substances secondary. Mayer bases his assumption upon the fact that at least a part of the grape-sugar becomes katabolized via glycuronic acid, and that further oxidation—in part, at any rate—would carry it through the stages glyconic acid, saccharic acid, and oxalic acid. The question is of great importance to diabetes, in that Mayer regards a defect in the further oxidation of glycuronic acid as the first sign of a disturbance in carbohydrate metabolism. True diabetes would be the result of a further development along the same line, until a point is reached at which the original carbohydrate molecule is incapable of any oxidation at all. The oxidation might stop at the stage of oxalic acid; and perhaps this explains the increased oxalic acid so often found in diabetes (see below). As further evidence in favour of his view, Mayer quotes cases in which the glycuronic acid was increased, though the aromatic substances were no more abundant than usual. Phloridzin diabetes is also explained with ease upon his theory.

When we come to review the fundamental facts, we find that we do not possess a sufficient number of statistics upon the amount of glycuronic acid in diabetic urine. We only know that it is increased. The reason for the lack of definite figures is, of course, the extreme difficulty of estimating glycuronic acid accurately. We are on this account prevented from putting P. Mayer's hypothesis to the test. That glycuronic acid is increased in diabetic urine is certain, but there are no grounds upon which to explain this upon different lines to the increase of glycuronic acid in other diseases. We are unable to explain it any more than we can the presence of lævulose and dextrin. What we need are exact observations in which the intestinal putrefaction, the quantity of aromatic substances, and the amount of oxalic acid, are all estimated at the same time. It is even likely that we do not yet know all the different substances which can combine with glycuronic acid to form compounds that will be excreted. It has recently been shown that acetone bodies probably have a weak affinity for glycuronic acid (aceton-glycosuria) [Ruschhaupt, Müller, Neubauer (201)]. If this be so, the foundation of Mayer's hypothesis begins to totter. Moreover, glycuronic acid given by the mouth becomes

completely oxidized, even in severe diabetes [Baumgarten (202)]; it would be remarkable if this should not also be so in the slight cases.

A few observers incline to Mayer's view [Wohlgemuth (203)], but many object to it because it has no real basis [Bial, Blumenthal, Esdall, Neubauer (204)]. It is a theory only; whatever doubts there may be about it can only be decided in the future.

B.—GRAPE-SUGAR.

As has been said, dextrose is the sugar which is chiefly concerned when we speak of glycosuria. We shall, however, say comparatively little about it here, because all text-books go fully into the matter. The biological basis of diabetic glycosuria was discussed at the commencement of this section.

1. Slight and Severe Forms of Glycosuria.

Different cases of diabetes exhibit varying degrees of inability to assimilate sugar. It is usual, therefore, in practice to distinguish *slight* from *severe* forms [Traube (205)].

(1) *Slight Glycosuria.*—The urine only contains sugar when carbohydrate is taken by the mouth. There are many degrees of this condition. Some cases only cease to pass sugar when carbohydrate is absolutely excluded from the diet. Others can tolerate 50, 100, or 150 grammes, but develop glycosuria when more is given. In speaking of carbohydrate diet, we mean particularly starchy foods, for it is these which are of chief importance in practice. Cane-sugar has long been banished from diabetic dietaries. Lactose and maltose have been just discussed.

For severe cases of glycosuria, Naunyn's classification is adopted:

(2) *Glycosuria of Medium Severity.*—This includes cases in which, besides carbohydrates, the albuminates must also be limited, so that the nitrogen in the urine lies between 10 and 18 grammes per diem [von Noorden (206)].

(3) *Glycosuria of Great Severity.*—This includes cases in which, even in the absence of carbohydrate food, sugar continues to be excreted, unless the protein be also greatly restricted, down to a point at which the nitrogen in the urine is less than 10 grammes in the twenty-four hours.

The above classification is not fundamental, but serves to subdivide cases for practical purposes. Seegen (207) attempted to show that there were two quite distinct forms of diabetes which had nothing to do with one another, etiologically or pathologically; but this view is no longer held. Not only is the passage of slight into severe forms not unusual, but almost every case of severe glycosuria has been slight to begin with, and has gradually advanced.

Until quite recently it was held that no case of human diabetes is so severe that every particle of sugar reaching the circulation is excreted in the urine. It is idle to discuss this question, seeing that protein and fat may produce sugar, and we do not yet know how much sugar is or can be

thus produced in health. The statement is usually true as regards the carbohydrates in the food [Külz, Troje, Leo (208)]. If a patient taking a fixed diet excretes an average quantity of sugar, A, and then an additional amount, B, of carbohydrate be given in the food, the urine usually contains less sugar than A + B—that is to say, the body has burned up a part of the additional carbohydrate.

I believe I was the first to record a case in which this law did not hold good [von Noorden (209)]; the whole of the additional carbohydrate at once reappeared in the urine. This is also the case in the diabetes which follows total extirpation of the pancreas [Minkowski (51)]. I have since found that in cases of moderate and of great severity it is no uncommon thing for the whole of the carbohydrate A + B to appear in the urine, though possibly not upon the very first day. If one continues to give the additional amount B, the excretion often exceeds the value A + B after two to three days. Rumpf found this confirmed by notes of cases under the care of Külz (210).

2. Influence of Various Carbohydrates.

(1) *Different Varieties of Sugar.*—The effects of these have already been discussed.

(2) *Derivatives of Carbohydrate.*—Of recent years experiments have been made with many substances which may be intermediary products of carbohydrate katabolism. Diabetic patients deal with *d*-glyconic acid, *d*-saccharic acid, muconic acid, glycuronic acid, glycosamine hydrochloride, succinic acid, *d*-acetic acid, much as they do with sugar [Baumgarten (202)]. The same was formerly held with regard to lactic acid [Cantani, Weintraud, Naunyn (210A)]; but perhaps this is wrong. In a few very severe cases of diabetes which I lately investigated with regard to this point, lactic acid seemed to cause a great increase in the glycosuria; this needs further testing. If it were so, it is of great theoretical importance; in practice it concerns us less, since anything like a large quantity of lactic acid often produces diarrhœa, and therefore cannot be given.

(3) *Starchy Foods.*—Different starches do not seem to act in the same way upon glycosuria. The effects of 60 grammes of starch, for example, may be very different according as it is given in the form of bread, or of oats, or of potatoes. The posthumous notes of Külz, published by Rumpf (210), afford many useful examples of this. Whether it depends upon any peculiarities in the different kinds of starch, or whether it is due to any of the different substances that are associated with them, is almost unknown. Mossé adopts the latter view, and thinks that of all starchy food-stuffs, potatoes have the least harmful effect on the glycosuria (211). He believes this to depend upon their richness in potassium salts. My own experience is that oatmeal is even better still [von Noorden (212)]. I have found that many diabetics, particularly severe cases with marked acetonuria, excrete much less sugar when they eat large quantities of oatmeal than when they are put upon the strictest diet which is as free from carbohydrate as is technically possible. Many

patients who on the strictest diet were excreting 50 grammes of sugar or more almost or entirely ceased to have glycosuria when put upon the oatmeal diet. The latter usually consisted of 250 grammes of oatmeal, 300 grammes of butter, 100 grammes of vegetable protein, and seven or eight eggs. As a proof that the carbohydrate was actually katabolized in the body, the acetonuria diminished greatly, often from several grammes to a trace. The fæces of these patients contained no more carbohydrate than normal. I have brought forward the hypothesis that the peculiar constitution of oat-starch may be the cause of its better utilization. There is one more point before we leave the subject. Preti (213) has, at my instigation, investigated several patients who were undergoing the oat cure to see if the blood contained substances which exerted a specific diastatic action upon potato-starch, as Ascoli had found to be the case after feeding with other starches such as rice and potatoes. The results were entirely negative.

Lipetz (215), supported by Ewald, Sigel, Langstein, and Lüthje (214), has thrown doubt upon both the practical and the theoretical value of the oat cure, but I think his experiments were quiet inadequate. He found that, upon oat diet, the number of bacteria in the fæces was much increased, and he expresses the opinion that the oatmeal starch led to so little glycosuria because the carbohydrates had undergone bacterial disintegration in the intestine. This objection is at once overthrown by the coincident diminution in acetonuria [von Noorden (216)].

Schade (216A) brings forward an idea that is full of possibilities. The seeds of different Graminaceæ have different effects upon the *Flammenbrennbarkeit* of cane-sugar. Schade thinks this may depend upon variable katalytic substances in the seeds, and he expects that a further investigation of the phenomenon will throw light upon the different effects that various starches have upon glycosuria. I can only say that I am unable to see how these physical phenomena and the biochemical processes are to be connected.

The remarks that I have made as to the effects of the oat cure bring before us new facts. We cannot expect to explain them before we know more about the intermediate stages of carbohydrate metabolism.

Another remarkable fact is that cane-sugar is often far better dealt with by diabetics when it is injected *per rectum* than when it is given by the mouth (217). Allowing for the fact that only about half the sugar injected into the colon is absorbed, Orlowski, working in my ward, found :

	Case I.		*Case II.*		*Case III.*	
	Sugar.	Acetone.	Sugar.	Acetone.	Sugar.	Acetone.
	Gm.	Gm.	Gm.	Gm.	Gm.	Gm.
No glucose added	17·3	0·68	9·9	0·30	26·6	1·70
100 grammes glucose *per rectum*[1]	10·6	0·33	27·3	0·30	22·9	1·52
50 grammes glucose *per os* ..	34·8	0·61	26·9	0·36	41·9	1·63

[1] We always gave double as much dextrose *per rectum* as *per os*, because it has been hown that about half the sugar injected in an enema is expelled again.

In Cases 1 and 3 the difference is very striking. Whether or not the explanation is to be found in rectal fermentation of the glucose is still doubtful, in spite of further investigations instituted to decide this point. The only fermentative change seems to be in the direction of lactose.

3. The Influence of Albuminates upon Diabetic Glycosuria.

I would only recall the fact that different albuminates have different effects. As Külz (218) pointed out, and as practical experience has demonstrated times without number, the influence of albuminates in increasing glycosuria is most marked in severe cases of diabetes, though it can be seen to some extent in slight cases also. Much more time is needed in these investigations than is usually devoted to them. In the mild cases we have no such exact records as we have in the severe. Practical experience teaches us that diabetics with but slight glycosuria develop and maintain a higher degree of toleration for carbohydrates when their proteid food is limited [Naunyn, Lenné, Kolisch, von Noorden (219)].

4. The Influence of Fat upon Diabetic Glycosuria.

See p. 555.

5. The Influence of Alcohol upon Diabetic Glycosuria.

The first exact experiments upon this question were made by Külz (220). The glycosuria was not increased. This has been thoroughly confirmed by the elaborate work of Hirschfeld, and I have found the same. This applies to ordinary medical doses. It is very different with acute alcoholic excesses and with chronic alcoholism. These create a tendency to glycosuria [von Strümpell, H. Strauss, J. Strauss, Reuter, Hoppe-Seyler, (222)]. As Langstein (223) points out, and as I myself can confirm, the acetonuria often diminishes when alcohol is given boldly. This is not, however, true in all cases.

6. Influence of Muscular Work upon Diabetic Glycosuria.

Muscular work, as a rule, increases the katabolism of sugar, and to that extent diminishes the glycosuria, provided the diet remains the same [Külz, Bourchardat, Zimmer, von Mering, Finkler, Albu (224)]. This fact is of great practical importance, and is applied as a therapeutic measure. Theoretically, however, it is more interesting and important that there are exceptions to this rule [von Noorden (225)]. Külz gives three such cases, which seem to have been entirely lost sight of. His posthumous papers also contain examples [Külz, Rumpf (210)]. I should here like to give the notes of six observations of my own upon the point in question. All six patients were suffering from severe glycosuria, but they were bodily strong, and were not fatigued by marching. On the work days a journey to Feldberg in Taunus was performed, which meant four and a half hours' walking, including a climb to the height of 660 metres. The diet was free from carbohydrate, and was the same both on work and

rest days. The figures for rest days are the average glycosuria on the day before and the day after a marching day. Water was drunk *ad libitum*. On the rest days the patients kept their rooms.

Case.	*Rest Day.*	*Walking Day.*
	Gm.	Gm.
1	29·8	31·3
2	40·2	45·6
3	12·8	19·2
4	28·9	39·5
5	43·7	51·6
6	46·9	49·2

The first of the above patients repeated the experiment later, with this difference : that he now walked for three hours on five consecutive days, and then rested on the five days immediately following. The diet was strict, but with the addition of 50 grammes of bread per diem. During the marching period he excreted 99·2 grammes of sugar daily, and during the time of rest 92·5 grammes. The estimations were by Allihn's gravimetric method. The nitrogen excretion was constantly 15·6 to 14·9 grammes per diem throughout. For the importance of these observations from a theoretical point of view, see p. 544 *et seq.*

We must give a few examples of the converse state of affairs.

Case.	*Rest Day.*	*Walking Day.*
	Gm.	Gm.
1	29·4	8·7
	32·4	23·8
	34·0	22·2
2	28·6	17·7
3	6·1	0·0

In Case 1 the urine contained :

	Acetone.	*Ammonia.*	*Nitrogen.*
	Gm.	Gm.	Gm.
Rest days	0·34	1·1	10·3
Walking days	0·41	1·2	11·8

In Case 2 the urine contained :

Rest days	1·04	—	—
Walking days	0·77	—	—

The diet was strict, except in Case 1 where the following additional allowance was made per diem :

	Gm.
Cream	200
Oatmeal	30
Potatoes	75

Heinsheimer (225A) has recently reported some interesting results he obtained in dogs suffering from pancreatic diabetes :

Case.	*Rest Day.*		*Work Day.*		*Calorie Value of External Work.*
	Sugar.	Nitrogen.	Sugar.	Nitrogen.	
	Gm.	Gm.	Gm.	Gm.	
1	23·15	12·50	17·60	12·60	63·9–147·3 calories.
2	18·00	5·13	9·35	3·45	53·2 calories.

The actual increase of katabolism due to the muscular work was, of course, at least three times the above—that is to say, 192 to 442 calories in the one case, and 160 calories in the other. The diminution in sugar eliminated will by no means account for all this : 5·55 grammes = 22·7 calories, and 1·68 grammes = 6·9 calories. The experiments show the muscle cells had for the most part lost their power to make use of sugar, and, judging from the nitrogen in the food and in the excreta, the work must have been done at the expense of fat.

Salomon investigated the respiratory quotients of some of my patients. After a control without food, the first man—

(1) Received 100 grammes of grape-sugar.

(2) The second observation during rest was started forty-five minutes later, and lasted half an hour. Then another 70 grammes of grape-sugar were given, and half an hour later there followed :

(3) Work for fifteen minutes.

In the fasting state the urine contained 4·0 per cent. of dextrose ; this rose during the experiment, after giving the grape-sugar, to 6·8 per cent.

The second patient received strict diet plus 100 grammes of bread daily. The observations were made two hours after midday dinner, which consisted of meat, green vegetables, 25 grammes of butter and cheese.

	O_2 per Minute.	*CO_2 per Minute.*	*Respiratory Quotient.*
1. Diabetes gravis :	c.c.	c.c.	
(*a*) Rest	251·5	174·3	0·692
(*b*) Rest (after dextrose) ..	266·5	179·9	0·674
(*c*) Work with ergostat ..	1211·7	823·0	0·679
2. Diabetes gravis :			
(*a*) Rest	282·0	220·8	0·783
(*b*) Work with ergostat ..	1295·3	907·5	0·700

7. Variations in the Intensity of the Glycosuria.

The inability of the tissues to katabolize carbohydrate is by no means constant in the same individual. In the course of every case of diabetes there are periods of more and periods of less glycosuria, corresponding with a worse and a better general condition respectively. The variations are in part dependent upon treatment, but also occur quite independently of this. It is a well-established fact that a strict diet continued over a considerable period may greatly increase the tolerance of the diabetic for carbohydrates. In milder cases this effect lasts a long while ; in severer cases it soon passes off. From amongst a large number of instances I pick out the following, as an example of how systematic dieting may have a good influence for a long while afterwards :

	Average Sugar in Urine per Diem. Gm.
5 days' strict diet + 120 grammes of bread	23·2
14 „ „ without any addition	0
	(Traces on the first two days only)
5 „ „ + 60 grammes of bread	0
5 „ „ + 100 „ „	0
5 „ „ + 120 „ „	0
5 „ „ + 140 „ „	0
5 „ „ + 160 „ „	0
	(On the first two days, traces; thereafter, none)

8. Influence of Intercurrent Febrile Diseases.

Intercurrent diseases often produce great diminution in the glycosuria. In great part this depends on decrease in the intake of food. Nephritis is the only condition in which the diminution may occur apart from change in the diet. Much more frequently the intercurrent affections increase the glycosuria. This is particularly the case after severe injuries, and with inflammatory skin diseases, furunculosis, and gangrene. The detailed discussion of these conditions belongs to clinical medicine, and not to a chapter upon the Metabolism of Diabetes (see the text-books of Naunyn, von Noorden, Williamson, and others).

We will, however, discuss the effects of febrile disorders a little more fully here. The older writers almost all taught that acute infective diseases were extremely dangerous to the diabetic patient, because his powers of resistance were so low, but that during certain of them, such as recurrent fever, typhoid fever, pneumonia, and erysipelas, the glycosuria diminished markedly. There undoubtedly are such cases [Schupfer, Hirschfeld (226)]. Recently, however, so many observations, more careful than earlier ones, and including analyses of the fæces, have shown the reverse to be the case, that one is bound to doubt the accuracy of the older experiments [Bussenius, von Noorden, Hirschfeld, Naunyn, Mohr (227)]. These new observations agree better than the older ones with the fact that non-diabetics also show a considerable tendency to alimentary glycosuria during highly febrile disorders [von Noorden, Poll, de Campagnolle (228)]. The connection between these two facts, which are obviously related to one another, is not perfectly simple. It is known that the stores of glycogen in the body diminish during fever [Manassein, May, Hergenhahn, Rolly (229)]. The liver loses it first [May, Rolly], but later the muscles are affected in the same way. From experiments which Hergenhahn carried out at my instigation, it now appears that it is less a question of increased katabolism of glycogen to supply the additional disintegration in the body than one of diminished power of the organs to form and store up glycogen; in this respect it is like true diabetes. If this view be correct, it is easy to understand the tendency to alimentary glycosuria during fever, and the increase in the diabetic glycosuria that pyrexial affections cause. The disturbance in glycogenesis seems to depend more upon the degree of pyrexia than upon the nature of the infection. It may occur as the result of simple pyrexia following puncture of the so-called heat-centre [Rolly]; hyper-

glycæmia has been found in such cases [Noel Paton, Richter (230)] exactly as after Claude Bernard's *piqûre*. Richter propounded the idea that in fever two opposite factors are at work in regard to hyperglycæmia: that the pyrexia itself tends to produce hyperglycæmia and glycosuria, whilst the bacterial toxines produce the opposite effect; so that, according to which of these two factors predominates, there is an increase or a diminution of the glycosuria in a diabetic who is suffering from an intercurrent fever.

Probably the nature of the infection is of importance. For example, Kaufmann and Charrin (231) found that the percentage of sugar in the blood fell after inoculating animals with *Bacillus pyocyaneus;* whereas after anthrax infection the liver loses its glycogen, and hyperglycæmia appears[1] [Colla (232)]. In the same way, Nebelthau (233) found that different bacteria had very different effects upon the glycosuria of animals whose pancreas had been ablated. Whether the injurious effect of the febrile infection, regarded as a whole, is exerted indirectly through the pancreas, or directly upon the glycogenic function of the liver and muscles, is a question not yet ripe for discussion.

Richter's hypothesis may account for the phenomena whilst the infective disease is in full swing, but it does not explain why acute febrile disorders, particularly influenza and streptococcal tonsillitis, leave behind them a temporary, and often permanent, exacerbation of the diabetes [von Noorden, Hirschfeld, Pavy, Mohr (234)]. It is difficult to explain this in any other way but as the result of direct damage to the pancreas.

It must also be mentioned that Lüthje (234A) found the glycosuria of dogs which were suffering from pancreatic diabetes to be much less when the external temperature was high (22° to 24° R.) than when it was low (8° to 10° R.). He gives no figures upon the temperature of the blood in these cases.

V.—ACETONE AND ALLIED BODIES, AND DIABETIC INTOXICATION (DIABETIC COMA).

1. The Sources of Acetone Bodies.

The close relationship between acetone bodies and carbohydrate metabolism has been fully discussed in another part of this work. Its great importance in any theory of diabetes goes without saying. Every change in our knowledge and theories about acetone bodies affects diabetes also. I need not here go into the history of acetonuria and the older views upon its origin. I refer the reader to the researches of Magnus-Levy, Waldvogel, Mohr, and Satta (235), and to Vol. I.

Acetone is a by-product of protein. This was first shown *in vitro;* the site and mode of formation of acetone from derivatives of protein in

[1] Spontaneous hyperglycæmia (0·136 per cent.) without glycosuria was also found by us in lobar penumonia at the height of the disease. The administration of 100 grammes of grape-sugar raised the sugar in the blood to 0·28 per cent., yet no glycosuria ensued. The hyperglycæmia must have been counteracted by a greater impermeability of the kidneys, produced by the febrile process.

the body were worked out in my laboratory (236). Embden and Kalberlah, in transfusion experiments upon recently excised viscera, recognised that the liver is the only organ which yields acetone on transfusion with normal blood. The amount of acetone formed during an experiment varied between 12 and 27 milligrammes per litre of blood.

It was proved that the addition of various substances, amongst them derivatives of protein, to the blood increased the amount of acetone produced [Embden, Salomon, Schmidt]. The following were particularly active in forming acetone : leucin, isovalerianic acid, butyric acid, the higher homologues of the latter which contain the same number of carbon atoms, β-oxybutyric acid, and certain aromatic substances whose benzene ring is destructible in the body, such as tyrosin, phenyl-alanin, phenyl-α-lactic acid, and homogentisic acid. Embden, upon chemical grounds, came to the following conclusions :

1. The katabolism of aliphatic monamido-monocarbon acids takes place in such a way that they give up CO_2, lose their amine group, and become bodies containing one less carbon atom, probably the corresponding fatty acids.

2. After this change into fatty acids, they are further katabolized in the usual way, by oxidation, down to β-carbon compounds.

3. The katabolism of the aromatic nuclei was not fully explained, but acetone was proved to be a product of the benzene ring when the latter was split up. Probably homogentisic acid is an intermediate product between the benzene ring and acetone, just as Neubauer and Falta (236A) showed it to be between tyrosin and phenyl-alanin.[1]

In showing that acetone is derived from protein via fatty acids, Embden and his confrères have settled the old dispute as to whether acetone is derived from protein on the one hand, or from fatty acids on the other hand. It has already been mentioned that the same experiments succeeded in referring sugar-formation from fat and that from protein both to the same chemical process.

Perhaps one of the most important of all the points which Embden and Kalberlah brought out is the fact that the same organ—namely, the liver—is the site of formation both of acetone and of sugar from fat and from proteid derivatives. The disorder of carbohydrate metabolism and the abnormal formation of acetone having a common locality, it becomes much easier to follow the chemistry of the condition.

Whether the acetone is formed entirely from protein, or whether it is also possible for it to be derived from sugar via glycuronic acid [Flückiger, Baer (237)], it remains probable that the greater part of the acetone bodies have fatty acids as their immediate precursors. Hirschfeld (238), continuing some earlier work of Rosenfeld's (239), discovered the fundamental fact that it is not increased protein katabolism, nor destruction of tissue protein, nor the limitation of the number of calories the food contains, which are the essential factors in causing acetonuria, but that the latter is due to the absence of proper carbohydrate metabolism. Since Geelmuyden, Magnus-Levy (240), and subsequently many others, showed that fatty acids, especially the lower ones, were quanti-

[1] For details, see the original articles by Embden and his colleagues.

tatively the greatest source of acetone bodies, the general conclusion seems to be : that when fatty acids are katabolized in the body without a certain quantity of carbohydrate being katabolized along with them, the conditions are extremely favourable for an increase of the acetone bodies above their normal very small amount.

It is not known how the carbohydrates are able to inhibit the production of acetone in this way. Our knowledge of the katabolic changes in carbohydrates and fats are still too imperfect for us to be able to say at what stage of this katabolism the inhibition occurs. We do not even know whether or not the acetone and allied bodies are really normal intermediate products of fat katabolism, or whether they are only formed when no carbohydrate is being broken down along with the fat. It is conceivable that some process of "secondary oxidation" occurs, such as Nasse long ago described (241).

It is not only possible, but probable, that oxybutyric acid is a regular and normal precursor of the acetone, undergoing immediate further oxidation. The healthy body is able to katabolize the acid completely when it is administered along with carbohydrate [Geelmuyden, Waldvogel, Schwarz (242)]. Acetone, on the other hand, is katabolized with extreme difficulty when thus administered by the mouth [Schwarz, Geelmuyden, Müller (243)].

The acetone produced in the body behaves differently. It is perhaps being produced all the time in health, probably from leucin [Embden and Almagia, G. Embden, H. Salomon, and F. Schmidt (236)] ; but in the normal body it is at once oxidized *in statu nascendi* in the living liver, whereas an artificially transfused liver is unable to effect this. Whether or not acetone arises from the ordinary simple fatty acids in the normal body is another question.

On the other hand, it seems likely that oxybutyric acid is constantly being produced from butyric acid, and this in turn from the ordinary fatty acids with straight chains of carbon atoms. If this be so, then in diabetes under certain circumstances some factor must be at work to prevent the normal further oxidation of the oxybutyric acid.

The following formulæ may perhaps be regarded as the normal stages of katabolism :

1. CH_3
   |
   CH_2
   |
   CH_2
   |
   COOH

—*butyric acid*. From this, by addition of one oxygen atom to the β-carbon atom, we get :

2. CH_3
   |
   CHOH
   |
   CH_2
   |
   COOH

—*β-oxybutyric acid.* Here the roads of normal and pathological katabolism separate. Normally another oxygen atom is taken up, the chain breaks between the α- and β-carbon atoms, and by oxidation of the one half of the chain, and reduction of the other, two molecules of—

3. CH_3
   |
   $COOH$

   ———

   CH_3
   |
   $COOH$

—*acetic acid* are produced. These are very readily oxidized, taking up 8 atoms of oxygen to form—

4. $4CO_2$ and $4H_2O$
   Carbonic Acid. Water.

The inhibition of this process that we were speaking of seems to take place at the moment when two molecules of acetic acid ought to be produced by a splitting of the oxybutyric acid chain between the α- and β-carbon atoms. In place of this, the reduction of the second half of the chain is omitted, whilst oxidation of the first half goes on—that is to say, aceto-acetic acid is formed, and by the loss of CO_2 this becomes acetone.

The pathological formulæ would thus be :

2. CH_3
   |
   $CHOH$
   |
   CH_2
   |
   $COOH$

—*β-oxybutyric acid.* From this, by the taking up of one more atom of oxygen by the β-carbon atom, and the removal of water, we get—

3. CH_3
   |
   CO
   |
   CH_2 + H_2O
   |
   $COOH$

—*aceto-acetic acid.* This, in the usual way, then becomes :

4. CH_3
   |
   CO + CO_2
   |
   CH_3
   Acetone. Carbonic Acid.

Why carbohydrates should tend to make the katabolism follow the first path, and their absence cause it to pursue the second, is quite unknown.

When there are difficulties in the way of the first process, part of the oxybutyric acid is compelled to undergo the second, with the result that acetone and aceto-acetic acid appear in the urine.

If the difficulties in the way of the normal process are still greater, the alternative route is not adequate to the katabolism of all the oxybutyric acid, and more or less of the latter itself finds its way into the urine.

2. Peculiarities of the Ketonuria of Diabetes Mellitus.

In diabetes there is a special tendency to ketonuria, partly because the patient takes little carbohydrate, partly because he cannot properly utilize what he does take. He is in a much worse position than a non-diabetic patient who is fasting or is living upon protein and fat, for he is excreting the carbohydrate formed from albuminates. The sugar produced from protein can inhibit the formation of ketone just as well as regular carbohydrate can ; for acetonuria diminishes when protein katabolism increases [Rosenfeld, Hirschfeld, Waldvogel, Talma (245)], provided that the protein does not drive up the glycosuria, and thus do away with the inhibitive action that the protein sugar would exert. Since little attention is paid to this point, it may be well to give the following observations, which are some of many :

Initials of Patient.	*Nitrogen katabolized.*	*Sugar.*	*Acetone.*	*Ammonia.*
	Gm.	Gm.	Gm.	Gm.
W.	6·10	7·3	0·58	1·7
	15·32	82·7	2·14	3·0
M.	9·53	19·1	1·18	2·3
	16·62	54·7	2·90	3·4
A.	6·30	5·2	0·42	1·7
	17·25	60·4	1·76	3·8

The figures are the averages for three consecutive days. The diet was always free from carbohydrate ; the only variation was the amount of meat during the two observation periods in each case.

Borchardt (245A), starting upon the assumption that different proteins contained different amounts of sugar-forming constituents, tested to see whether they exhibited differences in their inhibitory power over ketone production. His observations in cases of diabetes led him to place them in the following order :

Protamine.
Histone.
Egg-albumin.
Pancreas.
Casein.

From above downwards these contain progressively decreasing quantities of monamino-acids, which are the producers of sugar ; and, accord-

ing to Bouchardt, their antiketoplastic power places them in this same order.

Bouchardt's results, however, are by no means clear enough to justify absolute conclusions. A new aspect is given to the question by Embden's researches, which show that the same group of atoms—leucin, for example—can act as a producer of sugar and as a producer of acetone, as an inhibitor and as an augmentor of ketone formation.

The facts that physiology teaches in regard to partial inanition are, upon the whole, applicable to diabetes. The more the tolerance for carbohydrates is impaired, the more do acetone bodies appear in the urine, and so on. Many of the known facts are explainable without having to suppose that there are special anomalies of metabolism peculiar to diabetes. When ketonuria is slight, acetone alone appears. This is mostly excreted in the urine, but considerable quantities may be given off in the expired air [Schwarz, Müller (246)]; as much as 20 to 40 per cent. of the total acetone excreted has been found in the breath. When the acetone in the urine reaches 0·4 to 0·5 gramme per diem, the ferric chloride test usually begins to show that aceto-acetic acid is also present. I have verified this in several hundreds of cases. Often at this point, but more usually when the acetone in the urine reaches 0·8 to 1·0 gramme, β-oxybutyric acid also begins to be detected; it is seldom absent when the acetone amounts to 1·5 grammes or more. The more of these two acids there are, the more does the proportion of expired acetone fall behind the total amount of acetone and allied bodies in the urine; but the absolute quantity thus expired may be considerable—witness the strong odour of it that pervades the atmosphere round some of these patients. In one case of Schwarz's (247) the average of three days gave the following figures:

Acetone in the urine	6·97 grammes.
Acetone expired	4·9 ,,
Oxybutyric acid in the urine	43·9 ,,

In another of his cases the average over a period of eight days was 19·2 grammes of acetone bodies, reckoned as oxybutyric acid. The proportions were:

41·2 per cent. as oxybutyric acid in the urine.
43·5 ,, as acetone and aceto-acetic acid in the urine.
15·3 ,, as acetone in the expired air.

The main laws of ketonuria can be learned without reckoning the acetone in the breath, but for detailed investigations in the future it is essential for the expired acetone to be estimated.

The amount of acetone bodies, expressed as oxybutyric acid, was formerly much exaggerated. Figures such as the 226 grammes per diem of Külz are obtained by faulty methods. It was Magnus-Levy (235) who insisted on this. As a rule, the oxybutyric acid does not exceed 30 to 40 grammes even in the worst cases; exceptionally, the figures may be higher [Weintraud, Schwarz, Geelmuyden, Magnus-Levy, and others (249)]. Several times in my own laboratory as much as 50 to 60 grammes were observed over considerable periods by the Magnus-Levy method.

There is no constant relation between the quantity of oxybutyric acid and the total amount of acetone and aceto-acetic acid in the urine. In milder cases the acetone preponderates. Hart cites a number of cases in which acetone is excreted without any accompanying diacetic acid; the higher the degree of ketonuria, the greater is the proportion of oxybutyric acid, so that in advanced stages of acidosis this usually constitutes two-thirds to three-quarters of the total acetone bodies present. It depends to a certain extent upon other factors, such as the amount of alkali given by the mouth. This has a marked influence upon the oxybutyric acid, sending it up—at least, temporarily [Magnus-Levy, Mohr and Loeb, Waldvogel, Schwarz (250)]—whilst the acetone is much less affected by alkalis. When it is affected at all, as in a case of Weintraud's (251) and in one of Magnus-Levy's (240), the alkali seems to cause a larger amount of aceto-acetic acid to be eliminated instead. There are cases on record, however, in which alkalis either had practically no influence upon the acetone bodies at all, or even caused their diminution [Mohr and Loeb]. There are still a great many points about diabetic ketonuria to be elucidated (see below).

Fatty acids increase ketonuria just as they do in non-diabetic subjects. It is the lower fatty acids—butyric, valeric,[1] caproic [Schwarz, Loeb and Mohr (252)], and perhaps also acetic [Satta (235)]—that have the greatest influence in this respect. In a patient in my wards 56 grammes of butyric acid caused an additional excretion of 22 grammes of acetone bodies [Loeb (252)], so that it appears, incidentally, as if butyric acid can be directly changed into oxybutyric acid.

As regards the dietary of diabetic patients, the injurious effects of the lower fatty acids are of no great account. Butter, however, occasionally contains so many of the lower fatty acids, either free or as triglyceride, that it may be as well to knead it well in cold water before it is given to the patient [von Noorden (253)].

The higher fatty acids, the triglycerides of which form the fats of our ordinary food, may also increase the acetone bodies, seeing that during katabolism they pass through the stage of butyric acid. Every 100 grammes of fat can produce about 28 to 30 grammes of butyric acid in the body (254). In the cases quoted by Waldvogel and others (254), however, it was only a question of a few decigrammes or a gramme, even when maximal quantities of fat were given; the condition, moreover, was but temporary, the butyric acid ceasing to appear after a day or two. Often there was no increase of ketonuria at all; according to my experience, the great majority of cases show none of any importance. It is easy to understand why this should be so. The giving of fat does not increase fat katabolism. Only at the very first is it possible that, by a sort of mass action, the destruction of fat may increase slightly at the expense of that of protein and carbohydrate. For the rest of the time the exhibition of fat only leads to food fat being katabolized instead of body fat. The latter probably behaves exactly like the former, as regards the production of acetone; evidence of this is

[1] This is true only of isovaleric acid, according to Embden's new and repeated researches.

afforded by comparative observations upon ketonuria in inanition and upon protein fat diet [Satta (235)]. Just as in the case of non-diabetic people, the positive influence of fat upon ketonuria is only seen when the carbohydrate katabolism is in abeyance, or is very greatly diminished. So long as a diabetic is assimilating and burning up some 80 to 100 grammes of carbohydrate, the giving of more fat causes no real increase in his ketonuria [Satta, Mohr (255)].

In diabetics, just as in non-diabetics, the production of ketones is inhibited by the starches and hexoses, not in proportion to the amount of them eaten, but in proportion to the extent to which they are utilized in the body. Diabetic patients, even at their worst, katabolize at least a portion of the carbohydrates they take, and this is of importance in their treatment. As I have said, oatmeal is oxidized fairly well in such cases, and I have had very favourable results from its administration. The following substances also have an antiketogenous action :

Albuminates, within certain limits.
Pentoses [Mohr and Loeb (250)].
Glyconic acid [Schwarz, Mohr (235)].
Glycerin [Hirschfeld (245), Satta (255)].
Citric acid [Satta (255)].
Lactic acid [Meyer, Satta (255A)], though my own observations do not altogether confirm theirs.[1]

It is important to complete the list of antiketogenous substances, of which there surely must be many more ; and this not only for therapeutic purposes, but also to learn at what stage of their katabolism the carbohydrates exert their inhibitive action.

In many respects the ketonuria of diabetics differs from that of non-diabetics in degree only, but in one respect the difference is so fundamental that we may say that the effect of absence of carbohydrate upon the formation of acetone bodies must be regarded as a specific disorder of metabolism in diabetes. This specific disorder, though exhibited in very varying degree in different patients and in the same patient at different times, is often so great that all the physiological laws of ketonuria seem to be broken :

1. There are diabetic patients who tolerate carbohydrate—at least, of certain kinds—so well, and absorb and oxidize so much (*e.g.*, 70 to 100 grammes per diem), that if they were not diabetic no acetonuria would occur ; and yet they excrete quite large quantities of acetone. A few examples[2] will serve to illustrate this (see table, p. 594).

2. Many diabetics respond to the change from mixed diet to one free from carbohydrate by developing marked ketonuria ; the latter does not disappear when carbohydrate is again given. The prognosis is then very

[1] The experiments tabulated upon p. 594 show a sharp decline in the amount of ammonia.

[2] In each of these cases the ferric chloride reaction was marked ; oxybutyric acid was present. The breath had a strong odour of acetone. The figures for acetone given in the last column of the table therefore represent but part of the total acetone excreted. They serve, however, for purposes of illustration. All the figures are the average of several days.

unfavourable. They behave like non-diabetic patients, but in greatly exaggerated degree.

Case.	*Carbohydrate—*			*Acetone in the Urine.*
	In the Food.	In the Urine: Analysis by Reduction.	Assimilated.	
	Gm.	Gm.	Gm.	Gm.
1	150	77	73	2·3
2	150	66	84	2·3
3	150	92	58	4·7
4	150	74	76	2·8
5	150	58	92	1·1

3. In other cases the ketonuria resulting from strict diet is temporary or absent, or falls considerably after an initial rise. This is quite different to the ketonuria of non-diabetics, and can only be explained by supposing that the removal of all carbohydrates improves the general condition, and alleviates the pathological condition which produces ketonuria.

In the following table the figures are the averages for three days. At no time was the ferric chloride reaction positive, though it would have been in a healthy person upon the same carbohydrate-free diet (see Vol. I.). I drew attention to this long ago when reporting a case in which 4·5 grammes of acetone were excreted after strict diet was begun, but in which the amount fell to 1 gramme and less within three weeks, though the same diet was continued all the while [von Noorden (256)].

Case.	*Strict Diet +75 Gm. of Bread.*		*Strict Diet.*					
			First Three Days.		Second Three Days.		Third Three Days.	
	Sugar.	Acetone.	Sugar.	Acetone.	Sugar.	Acetone.	Sugar.	Acetone.
	Gm.	Gm.	Gm.	Gm.	Gm.	Gm.	Gm.	Gm.
1	Trace	<0·1	0·0	<0·1	0·0	<0·1	0·0	<0·1
2	7·0	0·07	0·0	0·168	0·0	<0·13	0·0	0·08
3	10·1	0·12	2·0	0·11	0·0	0·08	0·0	0·09
4	25·1	0·21	5·2	0·18	0·0	0·19	0·0	0·11

Satta (235) published a most instructive case from my wards The patient, suffering from very severe diabetes, excreted 2·21 grammes of acetone bodies (reckoned as oxybutyric acid) upon mixed diet. On the first two days of strict diet the average was 19·1 grammes of acetone bodies and 141 grammes of sugar. Very large quantities of fat, sesame oil, butter, ox fat, pig fat, 150 to 200 grammes per diem, were given, and yet the ketonuria sank continuously, and on the eleventh to thirteenth days of strict dieting only 1·5 grammes were eliminated, along

with 114 grammes of sugar ; four days later the ketonuria had fallen to 0·8 gramme. Similar cases have been described by von Jaksch, Wolpe, Weintraud, and particularly by C. A. Herter and F. W. Pavy (256A).

4. In different phases of the disease, even when the diet and the amount of sugar katabolized are approximately constant, the ketonuria may show wide variations (see the following table). This cannot be explained by habit, although this certainly plays a part in diabetics, as it does in non-diabetics. The ketonuria sometimes rises and falls periodically, the diet remaining the same ; at other times it shows a gradual but continuous rise. " Habit " will not explain these changes.

Name.	*First Period.*			*Second Period.*			*Time between the Two Periods.*	*Diet.*
	Sugar.	Acetone.	NH_3.	Sugar.	Acetone.	NH_3.		
	Gm.	Gm.	Gm.	Gm.	Gm.	Gm.		
O. K.	0·0	0·405	—	0·0	0·060	—	3 months	Strict+50 grammes carbohydrate.
Ki. ..	20	0·51	1·4	23·1	0·91	2·5	6 ,,	Strict+50 grammes carbohydrate.
Bo. ..	42	1·2	1·5	49·1	2·61	3·8	18 ,,	Strict+50 grammes carbohydrate.
Go. ..	31	1·0	1·9	28·0	0·31	0·8	4 ,,	Strict, without carbohydrate.
An. ..	38	1·7	1·8	31·0	0·52	1·1	23 ,,	Strict, without carbohydrate.

5. Different patients, living the same kind of life upon the same diet, and katabolizing approximately the same amount of sugar, exhibit very different degrees of ketonuria. This is most evident in patients whose diet contains no sugar, in which cases it is easiest to be sure that the carbohydrate metabolism is practically the same in all. The same quantities of " inhibitive bodies " seem to have very different actions in different cases. Two examples will illustrate this :

The urine became free from sugar in Adolf S., aged fifty years, after four days' strict diet ; in Miss Anna R. after ten days' strict diet, with the addition of green vegetables upon two of them. After eight days' complete absence of sugar from the urine, both patients continuing upon strict diet, the urine analyses, upon a ten days' average, were as follows :

	Adolf S.	*Anna R.*
	Gm.	Gm.
Amount of urine	1530	1980
Nitrogen	16·8	13·5
Sugar	0·0	0·0
Acetone	0·08	1·1
Oxybutyric acid	0·0	15·0
Ferric chloride reaction ..	0·0	+
Ammonia	0·9	1·9

Two diabetic patients, both bodily strong, and of approximately the same weights (65 and 67 kilogrammes), had been having the same diet with restricted carbohydrates (250 grammes of meat, together with eggs, cheese, butter, and green vegetables) for ten days. Both were as nearly as possible in nitrogenous equilibrium, and the urine, under the strict régime, was free from sugar. They were both living under exactly the same external conditions, and were metabolizing the same quantities, not only of protein and carbohydrate, but also of fat. On the four following days successively the one excreted 25 grammes of acetone bodies in his urine, the other 1·2 grammes, reckoned as oxybutyric acid in each case.

Such differences as these cannot be explained by personal "idiosyncrasy." In one group we have the low figures for the ketonuria, corresponding exactly to those of healthy persons upon a proteid fat diet; in another the high figures due to the supervention of a specific diabetic disturbance of metabolism.

As my former assistant, Mohr (235), ably showed, everything points to the fact that the ketonuria of diabetes is, or rather can be, specific. I say "can be," because it is not every diabetic patient who exhibits the departure from the physiological laws in this way. When the departure does occur, it is not merely quantitative, but qualitative and fundamental.

We know that the disorder of carbohydrate metabolism in a diabetic may be of different kinds: (1) Inefficient oxidation; (2) defect in the power to form carbohydrate from fat; (3) defect in the power to form and retain glycogen from carbohydrate. These three anomalies of metabolism are unequally marked in different cases; the amount of ketonuria must vary considerably, according as one or another or all three of the above functions are out of order.

We cannot help thinking, moreover, that there must be a primary qualitative disturbance in the metabolism of fat. My pupil, Mohr (235), has insisted upon this. Waldvogel, Satta, Schwarz, and Geelmuyden (235 and 244) have independently adopted the same view. Geelmuyden holds that there are two paths that fat katabolism may follow—the one via acetone and its allies, the other via carbohydrate, to carbonic acid and water; but I should like to see investigations carried out to see whether or not the formation of acetone from fat is not closely related to the formation of sugar from fat. In my text-book upon "The Pathology of Metabolism" (1893) the belief was expressed that the formation of sugar from fat may be a "facultative process" of the animal body—that is to say, one which only comes into play when, from one cause or another, there is a dearth of carbohydrate. This occurs during starvation, and upon a proteid fat diet, and in severe cases of diabetes. If we adopt this view, the relation between the ketonuria of diabetics and that of non-diabetics becomes close, and the two are brought into line with one another. It also becomes easier to understand the inhibitive action of carbohydrates and other antiketogenous substances; they oppose the formation of sugar from fat, and thus prevent the acetone bodies from being produced at the same time.

The outcome of the discussion is therefore a fact and a hypothesis:

the fact is that the lower fatty acids always increase the acetone bodies; the hypothesis, that the higher fatty acids only do so when they are katabolized abnormally in order to produce sugar.

I think it has been quite established that not only the quantity of fat katabolized, but also the way in which it is used, is of importance. A diabetic patient with marked glycosuria, who had been for five days upon a strict and constant diet, excreted an average of 25 grammes of sugar and 20 grammes of acetone substances in his urine. A climb up the Feldberg to a height of 660 metres was followed by these figures: 18 grammes of sugar, 18 grammes of acetone bodies, and on the two succeeding days 25·7 grammes of sugar and 22 grammes of acetone bodies. The nitrogen metabolism varied between 16 and 19 grammes. The diet was the same throughout. We here see that muscular exertion rather diminished than increased the acetonuria. A few other examples have already been mentioned on p. 583. Hirschfeld (238) also found that muscular work had little or no influence upon the acetonuria.

The elimination of acetone bodies leads to a drain of energy from the body; thus, 1 gramme of oxybutyric acid has a heat-value of 4·536 calories. When one thinks how much combustible material is draining away as sugar also, one readily understands the difficulty there sometime is in maintaining the energy requirements of the body, and in preventing emaciation in spite of a copious supply of food. This is bad, but there is a yet worse side to the question of acetone formation.

3. Acidosis.

The most dangerous result of the formation of acetone and its allies is the flooding of the circulation and tissues with acids—a condition which we follow Naunyn in terming "acidosis." Stadelmann (257),[1] the discoverer of β-oxybutyric acid, was the first to recognise that diabetic coma was the result of this increased formation of acids, and the similarity to Walter's experiments upon the toxic effects of acids upon animals was at once apparent. This teaching was elaborated by Minkowski, Kraus, Naunyn, and Magnus-Levy (260), Lépine, Saundby, Williamson, von Mering, and von Noorden (261).

Oxybutyric acid is *par excellence* the cause of acidosis, though acetic acid, and perhaps a few other volatile organic acids, may assist [Rumpf (262)]. Many authors sought the toxic agent rather in precursors of β-oxybutyric acid; Sternberg and Grube (263) picked out β-amidobutyric acid as one of these. It is very doubtful, however, whether β-oxybutyric acid is formed from this; Magnus-Levy (264) regards Grube's evidence as inconclusive. However, even if it must be allowed that other substances, possibly precursors of oxybutyric acid, may be largely concerned in the severe toxic symptoms which constitute diabetic

[1] The newly-discovered urinary acid was at first thought by Stadelmann to be δ-crotonic acid; it was soon afterwards identified as β-oxybutyric acid by Külz and Minkowski simultaneously. We owe to Stadelmann the discovery that the increased ammonia in the urine of severe diabetes is combined with organic acid.

coma, it is oxybutyric acid itself which causes the actual excess of acid in the body, or acidosis.

The figures upon this point are quite clear. Considerable quantities of the acid have been found in the body. Hugounenq recovered 4·27 grammes from the blood of a diabetic patient; Minkowski demonstrated 0·22 per cent. in the blood; Magnus-Levy 0·15 to 0·22 per cent. in the viscera and in the blood (265).

The human tissues are able to protect themselves up to a certain point against an increased production of acids and their toxic effects, by neutralizing them with ammonia. Large quantities of the latter become combined with the acids and excreted in the urine.

It is true that it is not every diabetic who excretes more ammonia than corresponds to the composition of his food. In the great majority of slight cases one finds between 1 and 1½ grammes of ammonia in the twenty-four hours' urine, and the relation between the total nitrogen and the ammonia nitrogen is about $\frac{10 \text{ to } 12}{1}$. When the figures are a little higher than normal, the abundant meat diet usually affords a sufficient explanation [Schittenhelm and Katzenstein (265A)]. When the meat in the food is limited, the ammonia, as a rule, is as low as 0·7 or 0·5 gramme.

On the other hand, in severe cases it is not unusual to find from 4 to 6 grammes of ammonia in the urine per diem, continuing for weeks and months. Larger amounts still, such as 10 grammes or more, are only found when coma is imminent, and even then are exceptional. Stadelmann (257) once found 12 grammes per diem; the highest figure I myself have met with was 10·5 grammes; no less than 45 per cent. of the total nitrogen excreted was in the form of ammonia. The latter, even when it reaches a high figure, usually does not exceed 20 to 25 per cent. of the total urinary nitrogen.

When the ammonia amounts to more than can be reckoned upon as derived directly from the food, it becomes practically certain that the diabetic patient is excreting an abnormal quantity of acid. This has been well established by the researches of Stadelmann, Wolpe, and Magnus-Levy, and by the observations of many other authors in single cases (266). Magnus-Levy regards the ammonia as an index of the acidosis, and showed, from reported cases, that the quantity of ammonia in the urine was an approximate measure of the quantity of β-oxybutyric acid. Every gramme of ammonia in excess of the amount due directly to the food corresponds to about 6 grammes (6·12 grammes, to be exact) of β-oxybutyric acid.

This relationship only holds good, of course, when fixed alkali is not being given medicinally. When alkali is given, the ammonia excretion may drop tremendously [Wolpe, Weintraud, Magnus-Levy, Gerhardt and Schlesinger, Külz (267), and others]. The most marked example of the effect of sodium bicarbonate that I have seen was the following:

Without sodium bicarbonate the average of four days was 6·9 grammes of NH_3.
With 30 grammes of sodium bicarbonate the average of four days was 2·0 grammes of NH_3.
Without sodium bicarbonate the average of four days was 5·7 grammes of NH_3.

Usually, however, the effect of the fixed alkali is much less—for example, in a case of Gerhardt's and Schlesinger's :

With 20 grammes of sodium bicarbonate the average of four days was 3·03 grammes of NH_3.
Without sodium bicarbonate the average of four days was 4·45 grammes of NH_3.
With 20 grammes of sodium bicarbonate the average of four days was 4·19 grammes of NH_3.

In ten cases, where the ammonia excreted was 4 to 6 grammes, I found that the taking of 30 grammes of sodium bicarbonate per diem was followed by a 10 to 22 per cent. diminution in the ammonia. The diet remained constant throughout. The periods of observation were sometimes three, sometimes five, days. Only a small part of the ammonia that has once become combined with acid within the cells becomes set free again when the salt meets with fixed alkali in the tissue fluids. Fixed alkali therefore assists the washing out of the acid, and often leads to a sharp rise in the curve of oxybutyric acid in the urine. The following instance is given by Magnus-Levy (267A).

Day.	*Sodium Bicarbonate.*	*Acetone Bodies calculated as Oxybutyric Acid.*	*Ammonia Nitrogen.*	*Total Nitrogen.*
	Gm.	Gm.	Gm.	Gm.
1-3	15-18	43·2	3·13	12·3
4	109	93·3	2·96	16·5
5	102	107·6	1·54	21·4
6	45	57·0	1·90	16·4
7	36	45·8	2·85	20·7

The results of alkali treatment are easy to understand in theory, and if they do not always follow in practice, we must suppose that there is not an acid retention in every case in which there is an increased acid production. This may explain the cases in which, for months and years, the general condition remains good, although large quantities of oxybutyric acid are being excreted [Weintraud, von Noorden, Sandmeyer, Naunyn, and others (268)]. It is not the acid excreted which acts as a poison, but that which remains in the body, and therefore the alkali treatment is indicated by way of prophylaxis quite as much as it is when coma threatens ; in the latter case it is unfortunately often in vain. One must not expect too much from the alkali treatment. The formation of acetone bodies, the formation of acid, and, above all, the errors in katabolism of oxybutyric acid, cannot be prevented by giving alkalis.

Notwithstanding the protective power of the ammonia, actual diminution in the alkalinity of the blood and tissues may ultimately ensue. In slighter cases of diabetes the alkalinity of the blood does not differ from that of health, but in the late stages of the disease, and especially in diabetic coma, the alkalinity has been found lower than it is in any other pathological condition (269). There is no object in giving all the figures here. They were obtained by various methods, and are not at all comparable with one another. The figures that Magnus-Levy obtained in

three patients who were passing into coma are instructive. They show the progressive decrease in the alkalinity :

	I.	II.	III.
	NaOH.	NaOH.	NaOH.
	c.c.	c.c.	c.c.
First observation ..	361	298	324
Second ,, ..	234	—	362
Third ,, ..	144	124	154

Magnus-Levy found that the alkalinity of 100 c.c. of normal blood corresponded to 320 c.c. of the same NaOH solution.

Gamble, after extensive investigations upon the methods for determining the alkalinity of the blood, concludes that in the healthy adult the alkalinity is about 300 milligrammes of NaOH per 100 c.c. In diabetes his results varied between 200 to 280 milligrammes of NaOH per 100 c.c. (277A).

A very important and interesting question is whether this diminution in alkalinity is due only to increase of acid, or whether it may also be due to loss of alkali from the body. Blood, muscles, and glands give up none of their alkali in diabetic acidosis ; the ash still bears the normal relation to the nitrogen [Magnus-Levy]. Nevertheless, there is a diminution in calcium. Several observers [Böcker, Neubauer, Toralbo (270)] long ago found more calcium in diabetic than in normal urine. Van Ackeren, in Gerhardt's wards, was the first to carry out a complete experiment upon the balance of inorganic constituents in a severe case of diabetes. In 1893 I made the following observations, but did not publish them (271) : The patient excreted far more P_2O_5, CaO, and MgO in his urine and fæces than he took in his food ; the elimination of P_2O_5 was considerably higher than it should have been to correspond with the total nitrogen excretion. It was concluded that bone was being disintegrated. The loss of calcium in diabetic acidosis was shown by some experiments of Gerhardt's and Schlesinger's (267). When the daily intake of CaO was 0·81 gramme, and the diet was constant, a healthy man excreted 0·620 gramme of CaO, a diabetic patient 1·127 grammes. The corresponding figures for MgO were 0·312 gramme and 0·505 gramme, the intake in each case being 0·31 gramme. The administration of 20 grammes of sodium bicarbonate per diem hardly altered the total calcium excretion, but caused a great change in the proportions present in the urine and in the fæces respectively. Whilst the alkali was being given, 46·8 per cent. of the CaO was excreted in the urine ; when no alkali was administered, the CaO in the urine was 76·1 per cent. of the whole. The results obtained by von Limbeck, Tenbaum, and W. von Moraczewski agree with those of van Ackeren, Gerhardt, and Schlesinger. Dengler, working in my wards, carried out some experiments which showed that the administration of calcium, but not of sodium, can stop the loss of calcium in diabetic acidosis for some time. When there is no acidosis, the calcium metabolism of

diabetic patients is the same as that of ordinary people [Gaethgens (273)].

Although calcium and magnesium thus drain away, the body does not contain a smaller proportion of bases than it should; for, as van Ackeren found, phosphoric acid is excreted in excess along with the earthy alkalis. The bones atrophy as a whole. We know nothing about the cause of all this; it is hardly conceivable that the action of an acid will account for it.

The body, in proportion to its weight, has not been shown to lose alkali. Perhaps this might turn out to be otherwise if there were exact means of estimating the organic bases; in the meanwhile we can, by analysis, only detect the increase in acid, not the diminution in bases.

The extent to which the increase in acid and the diminished alkalinity of the blood and tissues (acidosis) is to be blamed as the cause of diabetic toxæmia is not yet at all clear, in spite of the most painstaking work upon the subject. Magnus-Levy, relying upon Krauss's (273A) summary of our knowledge upon the basic and acid capacity of animal tissues, thinks that the excess of acid must neutralize basic side-chains in the proteid molecules, and may thus throw the protoplasmic metabolism into disorder (235). When this has gone on up to a certain point, diabetic coma results, rapidly in some cases, gradually in others. The acidosis must at least be an important factor, seeing that the alkalinity is at its very lowest in this coma; and anybody who has watched the wonderful effects of sodium bicarbonate injection in such cases cannot but be convinced of this. The good effects of such infusion cannot be obtained in every case, it is true, but it is not at all uncommon for patients to be brought round from the deepest coma by it. No other therapeutic measure can produce the same result. Of course, it by no means proves that the excess of acid is the only deleterious factor leading to coma in diabetic patients who are producing acetone bodies. It is improbable that we already know all the poisonous substances which may be formed in the body as the result of the anomalies of metabolism in diabetes; there is plenty of scope for further research here. An attempt, for instance, has been made to explain the coma as due less to the quantity of acids formed than to their kind. This was led up to by some experiments made by Binz and Mayer upon the toxic and soporific action of the lower fatty acids, butyric and propionic (274). Such a soporific action has, however, not been found in the case of β-oxybutyric and aceto-acetic acids, which are by far the most abundant in diabetes [Frerichs, Albertoni, von Jaksch, upon aceto-acetic acid; Araki, Meyer, Sternberg, Zeehuysen, upon i.-β-oxybutyric acid; Minkowski, Schwarz, and Waldvogel, upon L.-β-oxybutyric acid (276)]. Recently, in my own laboratory, Wilbur (277) made some experiments upon rabbits, and found that, even after complete neutralization, β-oxybutyric acid exerted a toxic influence upon the central nervous system quite independently of any increase in acidity or diminution in alkali. These questions can only be settled by future research; at present we can only say that the doctrine that diabetic coma is due solely to an acid intoxication is not quite satisfactory.

VI.—UPON VARIOUS FEATURES OF THE URINE IN DIABETES.

Much that might come under the above heading has already been discussed elsewhere. Other points require to be but shortly dealt with here, since they are mainly of clinical interest, and are fully treated of in text-books of special pathology.

A.—THE QUANTITY AND THE SPECIFIC GRAVITY OF THE URINE.

The quantity of water is usually greater the more sugar there is. Sugar is a diuretic. The blood and tissues become depleted, and increased thirst results. The polydipsia is obviously a secondary phenomenon ; it almost always disappears when the glycosuria is controlled by dieting. A few diabetic patients continue to drink copiously, even after the glycosuria has diminished or ceased ; these naturally continue to excrete large quantities of water. Upon a free diet, containing unlimited carbohydrate, there may be 10 litres of urine per diem, and 5 to 6 litres occur quite commonly.

Nevertheless, there are great individual differences between the relative quantities of water and of sugar. In most patients, however, who are left to drink as much or as little water as they please, the quantity of urine obviously rises or falls according as more or less sugar is being eliminated. The sugar and the specific gravity curves show steeper gradients than do those of the quantity of water. In diabetes, unlike any other disease, the more the urine the higher is its specific gravity. Exceptions there are, of course, but the following figures are based upon the averages of a very large number of cases :

Quantity of Urine.	*Specific Gravity.*	*Sugar.*
C.c.		Per Cent.
1,500–2,500	1025–1030	2–3
2,500–4,000	1030–1036	3–5
4,000–6,000	1032–1040	4–7
6,000–10,000	1036–1046	6–9

There are also exceptions to the rule that sugar has a diuretic action. Many patients, especially those in advancing years, pass normal quantities of urine, though the glycosuria may be 3 to 4 per cent. Peter Frank described these cases long ago under the name of " diabetes decipiens." My own experience is that they are commoner than the text-books would have us think.

The relative quantities of urine passed during the night and during the day have been determined by Külz with the greatest care. His figures show that the bulk is excreted during the day. My own observa-

tions confirm this. We found, upon the average, that two-thirds of the urine was passed in the daytime, one-third at night. In this respect the polyuria of diabetes differs from that of granular kidney, of convalescence, and of heart failure treated by digitalis ; in these the nocturnal diuresis is more marked than that of the daytime [Quincke (279)]. This peculiarity in diabetes agrees with the fact that most of the sugar is eliminated within two to three hours after a meal, carrying with it increased quantities of water.

The rapidity of the excretion of water may, however, be less than it is in health. Pick put a diabetic and a healthy person upon the same diet, both as regards solids and fluids. The quantity of water in the twenty-four hours' urine was approximately the same in each, but there was this difference : that the flow of urine after drinking water set in sooner and was over more quickly in the healthy person than in the diabetic (280). This, however, is not the general rule ; usually there is " tachyuria " in diabetes mellitus, just as there is in diabetes insipidus.

There is little tendency to œdema in diabetes. When cardiac or renal complications supervene, and when in non-diabetics there would almost certainly have been œdema, in diabetics there is none. I have therefore been all the more struck by the fact that upon the " oatmeal cure " I have frequently seen considerable accumulation of water in the tissues as œdema. The latter disappeared on returning to a diet free from carbohydrate, when the urine flow increased without any obvious change in the sugar elimination ; and at the same time, just as in the clearing up of other forms of œdema, the night urine was now in excess of that passed in the day.

B.—NITROGENOUS SUBSTANCES.

1. The Total Nitrogen.

See previous sections for the total nitrogen in the urine and its dependence upon the nitrogen in the food (p. 569), upon the calorie deficit (pp. 567, 568), upon the amount of carbohydrate in the diet (p. 569), and upon the disintegration of tissue proteid (p. 570).

2. The Proportions between the Different Nitrogenous Constituents.

These depend largely upon how much or how little ammonia is being excreted.

(*a*) *Urea and Ammonia.*

When there is no acidosis, the urea nitrogen usually maintains its normal 80 per cent. of the total nitrogen, whilst the ammonia nitrogen is 5 to 6 per cent. (281). When protein is given abundantly, the absolute amount of ammonia rises. In the absence of acidosis, moreover, the relation between total nitrogen and ammonia nitrogen is the same in diabetes as in health, and is remarkably constant [Schittenhelm and

Katzenstein (282)]. It is, however, *possible* that pushing the proteid may increase the ammonia relatively as well as absolutely, as the following example shows :

The diabetes was moderately severe. Throughout the observations the diet was the same (strict + 60 grammes of white bread), with the addition of 200 grammes of meat (raw weight) and two eggs during the middle period. There was no ferric chloride reaction.

Day.	*Total Nitrogen.*	*Ammonia Nitrogen.*	*Urea Nitrogen.*	*Ammonia Nitrogen.*	*Sugar.*	*Diet.*
	Gm.	Gm.	Per Cent.	Per Cent.	Gm.	
1	14·2	0·91	81·7	6·3	22	
2	15·1	0·93	81·7		24·3	
3	20·0	1·50	78·2	8·0	30·1	+ 200 grammes meat and two eggs.
4	22·9	1·88	78·2		28·9	
5	17·1	1·15	80·6	6·7	21·8	

With increasing acidosis, provided fixed alkali be not administered therapeutically, the absolute and relative quantity of ammonia nitrogen is increased, so that it may be used as a measure of the acidosis. It is not unusual to find the ammonia to be 20 to 25 per cent. of the total nitrogen (283). It is rare to find the proportion higher than this when the proteid metabolism is kept moderately high, the total urinary nitrogen being 18 grammes or more. Camerer mentions 35 per cent. of ammonia nitrogen in one instance ; I myself once found as much as 45 per cent. On the other hand, when the proteid food is systematically restricted, as may be essential in the treatment of the case, the resultant acidosis may be more severe, and the ammonia may be increased, as in the following examples :

Case.	*Usual Strict Diet* (18–22 *Gm. Nitrogen*).			*Vegetable and Fat Diet* (5–6 *Gm. Nitrogen*).		
	N.	NH_3–N.	NH_3–N.	N.	NH_3–N.	NH_3–N.
	Gm.	Gm.	Per Cent.	Gm.	Gm.	Per Cent.
1	19·0	3·1	16·3	5·2	3·3	63·4
2	17·1	2·9	16·4	3·4	2·3	67·7
3	17·5	4·0	23·0	4·2	2·8	66·6

No one has yet succeeded in replacing absolutely all the urea by ammonia, either in experimental acid poisoning or in the worst stages of diabetic acidosis. For further discussion of the subject, see pp. 597 and 598.

(*b*) *Purin Bodies.*

Of all the other nitrogenous constituents of the urine, the uric acid has been chiefly investigated. The old teaching, that uric acid is dimin-

ished in diabetes, has long been given up. It was based upon analyses made by the unreliable Heinz method (284). The most recent researches afford statistics which show that the uric acid and the other purin bodies bear their normal relation to the quality and quantity of the food [Bischofswerder, Jacoby, Richter, Mandel, and Lusk]. The exhibition of food that is rich in purin bases sends up the excretion of purin bodies acutely, just as it does in health. For example, in a case of Lüthje's, the uric acid rose to 5·38 and 6·70 grammes after the administration of 1,250 to 1,500 grammes of pancreas (286). Laquer (287) made similar observations after giving "Wuk" (yeast-extract)—for example :

Before giving "Wuk" the uric acid was 0·738 gramme.
Whilst giving "Wuk" the uric acid was 1·222 grammes.
After ceasing to give "Wuk" the uric acid was 0·702 gramme.

Laquer records similar figures from healthy persons.

In order to determine whether or not a diabetic patient excretes abnormally large or abnormally small quantities of uric acid and purin bases, either as a rule or under any particular conditions, it is necessary to put him upon a purin-free diet, so that only endogenous purins appear in the urine. Then, with certain reservations (*vide* chapter upon Gout), it is possible to draw deductions as to his metabolism of nucleins, and an additional value is given to an investigation of his uric acid excretion.

My former assistants, Mohr and Kaufmann (288), carried out some work upon these lines, and found :

Disease.	*Purin Nitrogen.*	*Ratio of Uric Acid Nitrogen to Purin-base Nitrogen.*	*Remarks.*
	Gm.		
Slight diabetes ..	0·143	6·7	Average of 4 days.
Severe ,, ..	0·303	5·0	,, 4 ,,
,, ,, ..	0·328	—	,, 2 ,,
,, ,, ..	0·228	9·0	,, 3 ,,

I have had very large numbers of uric acid investigations made in diabetics upon purin-free diets. In milder cases the figures without exception have corresponded to those of health—that is to say, the uric acid in the urine was between 0·35 and 0·45 gramme. This was also the case in many patients whose glycosuria was severe, both with and without acidosis. In a few cases,[1] however, the figures for the endogenous uric acid were considerably higher than normal—*i.e.*, from 0·75 to 0·95 gramme as an average for four or five days ; in all cases purin-free diet was begun several days before the estimations were started. Unlike Mohr and Kaufmann, we made sure that the calorie value of the food was enough, or more than enough, to cover all the patient's needs. All the cases were in the downhill stage. With greater certainty than

[1] In one case recently under observation upon a purin-free diet for six days the figures for the purin nitrogen were 0·28, 0·36, 0·19, 0·31, 0·31, 0·34 gramme.

was possible for Mohr and Kaufmann to do, I should now like to express my opinion, based upon the above analyses, that in severe diabetes there is often a great disintegration of tissues which yield purin bodies (nuclei). I regard this as due to toxines. It does not run parallel with the usual toxic destruction of protein ; at least, I have been repeatedly convinced that the general nitrogen balance of the body may improve simultaneously with an increased excretion of nuclein derivatives [von Noorden (289)]. I found no pathological alteration in the relation between uric acid and the other bases.[1]

(*c*) *Creatinin.*

Creatinin is increased in diabetic urine up to 2 grammes per diem. This has long been known, and often confirmed (290). It readily follows from the conditions of nitrogenous metabolism in diabetics. The patient eats a great deal of meat, and, besides this, under certain circumstances, breaks down his own muscle substance. He does not excrete more creatinin than does a healthy man upon a purely meat diet [2·163 grammes according to G. Bunge (291)]. When the patient takes food that contains little creatinin, the figures are naturally less [Winogradow, Stopezansky, Senator (292)].

Folin (293) has recently shown that the creatinin, just like purins, in the urine has both an endogenous and an exogenous component ; the former exhibits variations in different individuals, but is very constant in any given healthy man. It would be extremely interesting to know whether or not the endogenous creatinin of diabetics ever shows considerable variations from the normal 0·4 to 0·6 gramme per diem.

(*d*) *Hippuric Acid.*

It was in diabetic urine that hippuric acid was first discovered in man. The observation was made by Lehmann (294), and many others have agreed with him that it may be abundant, and readily demonstrated in diabetes [Bouchardat (295)]. Protein putrefaction in the intestine is the source of part of the hippuric acid. Diabetics often eat freely of albuminates which can give rise to benzoic acid. As a rule, they also consume quantities of green vegetables, likewise a source of benzoic acid. In the analyses available no attention has been paid to the nature of the diet. We must wait for further observations which include this point before we can say that excretion of excess of hippuric acid is a characteristic anomaly of diabetic metabolism. In one case, given by Lewin (296), the quantity was 0·24 gramme per diem, an amount which this author has also found in healthy people.

[1] The numerous estimations of the alloxuric bodies in diabetic urine made by the Krüger-Wulff method are too unreliable to be of value (see, for example, the works of M. Jacoby, Bischofswerder, and Richter).

(*e*) *Residual Nitrogen.*

After allowing for the urea, ammonia, purin bodies, creatinin, and hippuric acid, there still remains some nitrogen in a number of other substances whose nature and proportions are as little understood in diabetes as they are in health. In one case of Jacobi's, suffering from severe diabetes with an average nitrogen excretion of 19·6 grammes, there was 6·5 per cent. of residual nitrogen. In a similar case of Mandel and Lusk's the residual nitrogen formed 14·3 per cent. of the total 20·7 grammes nitrogen per diem (285). In my own wards three cases of severe glycosuria and acidosis, whose diet was free from carbohydrate, had 9·7, 10·2, and 10·7 per cent. of residual nitrogen respectively, after deduction of the nitrogen present as urea, ammonia, and purin bodies.

(*f*) *Amido-acids.*

Many investigations have been recently carried out upon the question whether or not abnormal quantities of amido-acids appear in the urine in diabetes mellitus. The study of amido-acid excretion is full of promise as a means of demonstrating those qualitative changes in protein katabolism which probably play a greater part in diabetes than we have been able to measure hitherto.

Some observers are satisfied with determining the so-called " amido-acid fraction " of the urine—that is to say, the nitrogen which is not precipitated by phospho-tungstic acid after deducting the urea nitrogen.

The estimation of this nitrogen fraction is particularly difficult in diabetic urine, because the presence of sugar prevents the estimation of the urea by the Pflüger-Schöndorf method [Landau, Mörner (297)]. On this account, von Jaksch's statement that the monamido-acids are increased in diabetes loses its foundation.

The Mörner-Sjöqvist method is here preferable, although some work done by Satta (298) in my laboratory renders it probable that this process includes a portion of the amido-acids with the urea. Satta found no constant change from normal in the amido-acids in the urine of a diabetic man, or in that of a dog without a pancreas.

Emil Fischer and P. Bergell (299) introduced the β-naphthalin-sulpho-chloride process, by which it is possible to employ a direct test for the presence of amido-acids ; this has been largely applied to diabetic urines lately.

Abderhalden (300), using the β-naphthalin-sulpho-chloride test, found tyrosin in moderate quantity in the urine of a patient suffering from arterio-sclerosis, myocarditis, and diabetes.

Mohr (300) isolated β-naphthalin-sulpho-glycocoll from the urine in several cases of diabetes, but not in any greater quantity than Embden and Reese (300) had already found it in healthy urines in my laboratory.

It is nothing but a supposition on Mohr's part when he considers that after feeding a dog suffering from pancreatic diabetes with *d*-leucin, the nitrogenous substance which appeared in the urine was leucin-tripeptide.

Just as Abderhalden and Mohr found amido-acids apparently preformed in the urine in their cases, so Bergell and Blumenthal (300) were able to show with seeming probability that peptoid substances may occur in the urine of dogs after ablation of the pancreas. The question at once arises how far this may be due to the absence of trypsin, or how far it is to be attributed to a specific disorder of metabolism in diabetes. This question cannot yet be answered.

The urine of Bergell and Blumenthal's dogs contained a substance which was unlike tyrosin and like certain peptoids, in that it gave a strong Millon's reaction in the cold. When the urine extract was treated with strong hydrochloric acid, which converts peptoids into amido-acids, they succeeded in isolating tyrosin as a naphthalin-sulpho-compound.

These same observers (301) tell us of another interesting point—namely, the peculiar results of giving an inactive alanin preparation to a diabetic patient in coma.

Plaut and Reese (300), working in my laboratory, showed that after giving inactive alanin to a healthy person, *l*-alanin appeared in the urine. Bergell and Blumenthal, in their case of diabetic coma (301), gave doses of 15 grammes of *i*-alanin at a time, and recovered from the urine a naphthalin-sulpho-alanin, part at least of which consisted of the natural dextro-rotatory variety.

In a case of severe diabetes, investigated in my laboratory, the amount of naphthalin-sulpho-amido-acid recovered from the urine was no greater than that found in a healthy case. On two consecutive days it amounted to 2·66 and 2·41 grammes.

It will be seen that we know almost nothing about the amido-acid excretion in diabetes ; a thorough investigation of the matter is much to be desired.

(*g*) *Albuminuria*.

The published statistics upon the occurrence of albuminuria in diabetes are abundant, and show that some 25 to 35 per cent. of all diabetics have either temporary or permanent albuminuria. Slight and severe forms of the disease are affected almost equally in this respect. For complete summaries of the statistics, and of attempts to arrange the albuminuric cases into definite groups, see (302).

Nephritis, parenchymatous or interstitial, is a by no means uncommon complication of diabetes, but is not as frequent as is albuminuria. All clinicians are unanimous in the view that diabetic albuminuria, variable as it is, and often only slight, can be attributed to true nephritis in comparatively few cases. It is more than doubtful whether the slight hyaline degeneration of the epithelium found post-mortem can account for an albuminuria which may have lasted for years. In the absence of anatomical changes in the kidney, the albuminuria of diabetics is often described as " functional." Possibly the functions of the kidney become upset by the enormous demands made upon them in the elimination of water, nitrogenous substances, and sugar. It has also been suggested that acetone bodies may damage the kidneys, and render them more

permeable to albumin. The results of experiments upon animals have led to conflicting conclusions upon this point [Albertoni, Pisenti, von Jaksch, Dreschfeld, positive ; Baginsky, Schwarz, Ruschhaupt, negative (303)]. It is hardly right to regard the results of experimental excretion in animals, lasting but a short time, as parallel with the action of pathological factors in man, lasting months and years. The factors which may lead to albuminuria in diabetes are, theoretically, so numerous that it is a matter of embarrassment to pick out any particular one as more important than the rest [Schupfer (304)]. The albuminuria often disappears when one succeeds in alleviating the glycosuria and in improving the general condition of the patient by suitable dieting. This shows that the renal disorder which leads to the albuminuria is often an immediate consequence of the diabetes; it comes into direct line with the other degenerative changes in the viscera of diabetic patients. Under proper diet the albuminuria often disappears simultaneously with the cure of amblyopia, neuritis, furunculosis, pruritus, and so on. Last year I saw nine such cases. It has often been maintained that strict diet increases the albuminuria, and that the presence of albumin is a contra-indication to such dieting, but this is not my own experience. It only holds good in cases complicated by actual nephritis.

The so-called " coma casts " must be mentioned here. They were first noticed by Ebstein (305), and were studied again later by Külz and his pupils (306). Aldehoff found them in every case of diabetic coma he examined. Other authors agree with this (307). Naunyn (308) could not always find them ; I myself have looked for them in a very large number of cases of diabetic coma, and have only failed to find them once. These casts have a certain prognostic significance, in that they frequently appear just before the coma, and serve as an alarm signal. Their appearance, however, is not absolutely restricted to the period of threatened or actual coma. Aldehoff and Rumpf described cases where they occurred whenever the diet was very strict, but disappeared again when carbohydrate was allowed. This may have been accidental. We have looked for them in vain both in mild and in severe cases when the patients were upon the strictest diet. In other cases we have seen them appear and disappear again in a few days without any apparent cause, and without any direct relationship with the quantity of oxybutyric acid in the urine. Up to the present they have never been found where there is no acidosis. Külz and his followers, and Waldvogel, have on this account expressed their conviction that these casts result from the action of acids. There seems a likelihood that this view may be true, but it is not possible to state it as a definite fact. The casts have nothing to do with the intensity of the albuminuria ; on the contrary, they are often present when the albumin can only just be detected by the most delicate tests.

(*h*) *Ferments.*

Leo found an increase in the diastase in diabetic urine, and there was more in severe than in mild cases. The absolute quantity seemed to bear no relation to the amount of sugar excreted. Bendersky's

results were similar. Stadelmann did some work which showed that pepsin might be abundant. We have no knowledge as to why these ferments should be present. The matter has been fully discussed by Grützner (309).

3. Nitrogen-free Substances.

(*a*) *Sugar.*

See p. 572 *et seq.*

(*b*) *Acetone Bodies.*

See p. 586 *et seq.*

(*c*) *Lactic Acid.*

This occurs in the blood and in the urine in other pathological conditions, and in these may lead to a considerable increase in the excretion of ammonia, but in diabetes it falls quite into the background. Bouchardat (310) states that he has often detected it in diabetes, but his method was not suitable for the identification of lactic acid with certainty. I have been unable to find any more recent and reliable reports. It may be mentioned that Minkowski (310) isolated the acid on one occasion from the blood at the autopsy upon a patient who had died in coma ; but post-mortem findings do not necessarily show that the acid was there before death. Upon three occasions I myself have looked with the greatest care for lactic acid in the urine of severe cases of diabetes, but each time in vain.

It is very desirable that researches upon the occurrence of lactic acid in diabetes should be prosecuted further, especially after the administration of lactic acid or its salts ; for lactic acid plays a large part in the intermediate stages of carbohydrate metabolism. Theoretically, lactic acid should be anabolized into carbohydrate, and it is quite possible that the power to do this is wanting in severe cases of diabetes [Embden and von Noorden (114A)]. In several cases we found the glycosuria to be unaltered by the administration of 80 to 100 grammes of sodium lactate per diem even when the diabetes was severe. Nevertheless, I would refer the reader again to those few observations in which the glycosuria was undoubtedly increased (see p. 559).

(*d*) *Lower Fatty Acids.*

These have often been found increased in diabetic urine, particularly in severe cases in which abundant acetone bodies were being excreted at the same time. Rumpf (311) was the first to draw attention to this. He described one case of diabetic acidosis in which volatile fatty acids seemed to replace the β-oxybutyric acid. In other cases of his the volatile fatty acids were much increased. Strauss and Philippsohn (312). found more than twice as much volatile fatty acid in a case of diabetes with constipation as they did in a healthy person upon the same diet.

The figures given by Herter and Wakeman (see table, p. 626) are also abnormally high.

The volatile fatty acids have been regarded as enterogenous products of decomposition. Strauss and Philippsohn look upon them as such. They cannot, however, be brought into line with the aromatic constituents of the urine of intestinal origin, for they are probably derived from the carbohydrate in the bowel, or perhaps from the higher fatty acids, rather than from protein. The greater part is quickly oxidized by the tissues into CO_2 and H_2O ; a small residue may appear in the urine. The volatile fatty acids may, however, be derived from other sources. They arise during aseptic autolysis of viscera [Magnus-Levy (313)], and play an important part in the formation of acetone bodies from higher fatty acids, as Magnus-Levy said was possible, and as Mohr confidently asserted (235).

The transfusion experiments made by Embden, Salomon, Schmidt, and Marx (104A) throw light upon the question. It has been shown that butyric acid can be oxidized in the body to form β-oxybutyric acid. Butyric acid itself arises, as was shown in the same experiments, from all the higher saturated fatty acids with an even number of carbon chains, whilst the katabolism of higher fatty acids whose number of carbon atoms is uneven (rare in the animal economy) does not take the route via butyric acid, and therefore does not lead to the production of acetone bodies either. The work that has been done in my laboratory seems to show that the formation of acetone and allied substances from fatty acids occurs exclusively in the liver.

(*e*) *Oxalic Acid.*

Cantani (314) originated the doctrine that oxaluria is very frequent in diabetes. This view is based upon microscopical examinations of the sediment. This method has been shown to be very unreliable in the detection of an increase of oxalic acid ; even the facts reported by Cantani, and confirmed by Czapek (315) and Fürbringer (316) are not constant. I have made microscopical examinations of many diabetic urines, and have found anything like large quantities of oxalates only quite exceptionally, whether in slight or severe stages of the disease. Variations in the diet might well have accounted for the positive cases.

Quantitative estimations have been published by Kisch (317). The amounts varied between 5·4 and 14·5 milligrammes per litre. Normal controls showed 15 to 20 milligrammes per litre. The oxalic acid was, therefore, rather diminished. My pupils Mohr and Salomon (318) have published some very elaborate and exact determinations. These were made upon eleven cases, mild and severe, and have these advantages over previous records : that the quality and the quantity of the food were known, and that the periods of observations were long. Controls were obtained from numerous estimations in normal people under the same conditions, and upon exactly the same diet. The oxalic acid excreted by diabetics corresponded exactly with the quantities found in healthy individuals when the food was the same for both. The results obtained

by Luzzatto (319) confirm this, though they were mostly made for single days only. Von Moraczewski's figures also lie well within normal limits (320).

It seems, therefore, that although we must allow that a diabetic patient here and there may excrete abnormally large quantities of oxalic acid [Fürbringer, von Frerichs, Senator, Naunyn, and others (321)], nevertheless there are a sufficient number of exact statistics to prove that increased excretion of oxalic acid is not a characteristic of uncomplicated diabetes. Where it does occur, the cause must be looked for in the diet, in complications with other diseases, and so on; it is impossible to draw definite conclusions until we know more about the biochemical and nosological significance of oxaluria. Mayer (322) recently expressed his belief in Cantani's original doctrine—namely, that diabetic oxaluria depends upon incomplete combustion of sugar. He says that "when sugar is katabolized, part of it passes through the stage of glycuronic acid; part of the latter in its turn becomes oxidized to oxalic acid." These and other conclusions of Mayer's seem to me to be going much further than is justified by the facts we have before us at present.

4. Inorganic Constituents of Urine.

(*a*) *Pneumaturia.*

In rare cases of diabetes the development of gas in the bladder has been observed [Guiard, Duménil, Thomas (323)]. Müller (324) was the first to analyze the gas in such a case, and found it to be mostly hydrogen and nitrogen, with a little carbon dioxide and traces of methane. This is similar to what is found in the gas produced by butyric acid fermentation of sugar. The nitrogen, Müller supposes, had diffused from the blood. In a later case Senator (323) found the gas to be mainly carbon dioxide, due to alcoholic fermentation of the sugar by yeast which had entered the bladder. Schmitz (325) appears to have seen a case of this also. In one case of my own the gas was carbon dioxide, and the yeast cells were detected. Another case I only saw once in consultation, and the nature of the gas was not determined.

Pneumaturia is no specific disorder of metabolism; it is merely an accidental complication dependent upon infection of the bladder. The variety of gas formed will depend entirely upon the kind of infecting organism. Pneumaturia is more liable to occur in diabetics than in other patients, because sugar is more liable than any other urinary constituent to produce gas as a result of bacterial infection.

(*b*) *The Ash.*

There are plenty of statistics upon the excretion of inorganic constituents, but we are able to draw but little definite conclusion from them. As a rule, the quantity is greater than in health; this is fully explained by the greater intake of food. The SO_3 and P_2O_5 are particularly

increased owing to the increased consumption of meat and eggs, and in some cases owing to the pathological disintegration of tissue protein also. Figures such as 4 to 6 grammes for each of these acids are therefore not unusual. Broadly speaking, the natural parallelism between them and the nitrogen is maintained; Gaehtgens' comparative estimations in a healthy man and in a diabetic patient show this. Külz confirmed the fact (326).

Sulphuric Acid.—Mandel and Lusk's experiments (285) showed that for every 100 grammes nitrogen the SO_3 upon six consecutive days amounted to 14·0, 16·0, 16·4, 15·3, 15·4, 16·7 grammes. The figures are normal.

Some authors incline to think that the neutral sulphur is increased in diabetic urines. Reale and Velardi (327) found 30·5 per cent. of the sulphur to be in neutral combination in health. In diabetics their figures lay between 39 and 61 per cent., sinking considerably when the glycosuria was checked by limitation of the carbohydrate food. On the other hand, Harnack and Kleine (328) found 19·41 and 19·40 per cent. to be the limit in diabetes; whilst, using precisely the same methods, they found 19 to 24 per cent. in health. At present, therefore, we can give no definite decision in regard to the neutral sulphur in diabetic urine.

Phosphoric Acid.—The matter is different in the case of phosphoric acid. When there is no acidosis, the relation between total nitrogen and P_2O_5 has always been found normal (329). In cases of acidosis, however, the P_2O_5 goes up, so that for each 100 grammes of nitrogen there were, upon the average :

18·2 parts of P_2O_5 [Gerhardt and Schlesinger (267)].
20·1 ,, ,, [Rumpf (330)].
19·0 ,, ,, [Mandel and Lusk (285)].

The normal proportion should be 100 to 12·5 upon the same protein diet. On administering alkali, the P_2O_5 begins to fall behind the nitrogen in diabetes as in health. In Gerhardt's and Schlesinger's case 20 grammes of sodium bicarbonate reduced the proportion to 100 : 14·8. In a patient of mine who had marked acidosis the average figures for four-day periods were :

	Nitrogen.	*P_2O_5.*	*Ratio.*
	Gm.	Gm.	
Without alkali	18·1	3·62	100 : 20·0
With 20 grammes sodium bicarbonate ..	17·4	2·85	100 : 16·3
With 20 grammes calcium carbonate ..	18·7	2·58	100 : 13·8
Without alkali	19·1	3·63	100 : 19·0

We have already discussed the significance of the high P_2O_5 figures in diabetic acidosis. The excretion of calcium and magnesium is mentioned in the same place.

Chlorides.—As regards the chlorides, there are great individual variations [Külz, Tenbaum, von Moraczewski (331)]. The sodium chloride

often rises with the nitrogen to high figures, such as 30 grammes and more ; it is seldom below normal. Different diabetics take different quantities of salt with their food. No conclusions other than these are to be gathered from the facts observed.

It would be extremely interesting to know the exact balance of the inorganic constituents in diabetic patients. It is still an open question as to how far the abnormal production of acid leads to a " demineralization " of diabetics, and as to what constituents are affected. All researches hitherto have concerned themselves only with the relations between acids and bases in the excreta. Except for calcium and phosphoric acid, no experiments have been done in which the inorganic constituents of the ingesta have been analyzed at the same time.

VII.—THE BLOOD.

1. The Water in the Blood.

The factors concerned in the concentration of the blood—water, hæmoglobin, red corpuscles, protein—show no typical changes in diabetes. The numerous statistics proving this are cited under (332). The red cells in bad cases, just before the onset of coma, are said to have an increased resistance to hypotonic salt solution, possibly an important point in prognosis [Jakuschewsky (333)]. In the milder cases Meyer (334) found an increase in the eosinophile cells—4·7 to 6·25 per cent., instead of the normal 0·5 to 4 per cent. Though normal as a rule, the hæmoglobin, blood-corpuscles, and serum protein may diminish much more quickly than in non-diabetic persons when complications arise, or when any factor is at work leading to anæmia [Lécorché (335)]. On the other hand, considerable concentration of the blood has been observed in the terminal stage. This fact was pointed out by Leichtenstern (332), and has recently been again brought forward by Rumpf (336) as of great importance in explaining the coma. In one comatose patient he found only 73·25 per cent. of water in the blood, the normal being 78·9 per cent. In another case the blood at the autopsy contained the normal percentage (? as the result of saline infusion), but the viscera, particularly the liver, spleen, and brain, were 5 to 6 per cent. under their normal percentage of water. In my wards three cases of diabetic coma showed :

	Percentage of Water in the Blood.		
Before saline infusion	79·3	78·7	80·1
Before death	77·9	76·6	76·7

In one patient who was hovering on the brink of coma for eight days the percentage of water in the blood two days before coma actually set in was 78·2, and about twelve hours after unconsciousness was complete (three hours before death) it was 75·3 per cent. The patient had been eating and drinking whatever he wished, and was given 60 grammes of sodium bicarbonate daily from the time the threatening symptoms appeared, so that his urine was strongly alkaline. In this case, therefore,

coma came on when the blood contained the normal percentage of water. Magnus-Levy (337) also gives figures which show, contrary to Rumpf's theory, that concentration of the blood is not an essential factor in coma. It no doubt gives additional severity to the terminal symptoms. The concentration obviously comes about from the fact that diabetic patients continue to excrete much urine even when deeply comatose, and also expire as much water as usual in their air hunger, whilst the intake of water is greatly diminished. Perhaps there may be special lymphogogues at work in this autotoxic terminal condition, similar to what Grawitz (338) has demonstrated in many other infections and intoxications.

The molecular concentration, as measured by the lowering of the freezing-point of the blood, is not obviously altered in diabetes [Landau (339)].

2. Inorganic Constituents.

For the *fixed alkalis*, see p. 598. Even in diabetic coma they are not diminished relatively to the other constituents of the blood, notwithstanding the acidosis. Dennstedt and Rumpf (340) found a little less sodium than usual in the blood and viscera post-mortem. This is the more striking in that the patients had been given quantities of sodium bicarbonate before death. The potassium was increased. The explanation of this is not clear.

A good summary of the published analyses of the ash of diabetic blood, together with several new determinations, will be found in Erben's paper (340). The material collected by Rumpf and Erben, and criticised by them, shows how little we have learned so far, in spite of most painstaking and laborious researches.

Ammonia was found increased in coma by Winterberg (341)—3·78 milligrammes per 100 grammes of blood, instead of the normal 0·6 to 1·3 milligrammes.

The blood-serum in severe cases of diabetes has frequently been found to contain *iron* [Jolles and Winkler (342)]; this has been attributed to the destruction of blood-corpuscles and platelets containing hæmoglobin [Mitulescu (343)]. Gumprecht and Stintzing (344) had previously shown that the colour intensity of diabetic blood may be greater than corresponds to the hæmoglobin alone. Rosin and Jellinek (345) confirm this. They suppose that, besides the hæmoglobin, some other colouring matter containing iron is formed as well. Possibly this accounts for the increase in the iron in diabetic urine [Damaskin, Hoffmann (346)]. According to Hoffmann, normal urine contains 1·09 milligrammes of iron per diem upon the average; in diabetes he found 3·70 milligrammes, and in one exceptional case 22·02 milligrammes of iron. Jolles gives even higher figures—up to 0·108 gramme per diem. It is well known that the kidneys can excrete iron more easily when it is united with nucleo-proteids than when it is in the form of salts.

3. Alkalinity and Diabetic Acidosis.

See p. 597.

4. The Sugar in the Blood.

See pp. 532 *et seq.*

5. Glycogen.

Glycogen was found increased in diabetic blood by Ehrlich and Gabritschewsky (347). It was partly free in the plasma, partly within the leucocytes. Probably the cells store up glycogen at the expense of the sugar in the fluid around them. The free glycogen may be derived from white corpuscles that have disintegrated. No great stress can be laid upon the presence of this glycogen, for it is known to be a normal ingredient of the protoplasm of leucocytes [Hirschberg (348)].

6. Ferments.

1. *Glycolytic Ferment.*—See p. 561.

2. *Amylolytic Ferment.*—See p. 581. It may be added that Lépine and Kaufmann, Achard and Clerc (349), have recently found the amylolytic power of diabetic blood to be less than normal. The last two of these observers think any great diminution to be a sign of bad prognosis.

3. *Toxines.*—Lépine and Boulud (350) state that the blood of a dog recently rendered diabetic by extirpation of its pancreas can produce glycosuria when introduced into the tissues of other animals. They attribute this to the action of a toxine. The toxines are said to be in the serum, and not in the red corpuscles.

3. *Hæmolysin.*—Sweet (351) publishes researches in which he finds that the blood of dogs, after extirpation of the pancreas, has greatly diminished hæmolytic and bactericidal properties. He thinks this depends upon loss of complement.

7. Fat—Lipæmia.

The occurrence of very large quantities of fat in the blood plasma seems to be a phenomenon peculiar to diabetes. It was already well known in the days when venesections were common. It was not investigated in detail until comparatively recently, and even now the question is not fully understood. I need not here discuss every case that is scattered through the literature, seeing that Zaudy and Fischer (352) have collected all the papers that have been published upon the subject.[1] The clinical facts are simple and clear. As a rule, the percentage of fat in the blood is not actually higher than the normal limit, which, according to recent determinations by Bönninger and T. Rumpf (353), is something like 1 per cent. Only in the severest cases of diabetes, and when the toxic symptoms are grave, does lipæmia appear, and it does not appear always even then. Schwarz (354) says it only occurs when there is much acidosis, and apparently he is right. My own experience is similar to his.

When the lipæmia is marked, the serum is as though mixed with milk,

[1] Two observations should be added to this collection, namely: (1) Hale White, "Diabetic Intra-ocular Lipæmia" (the *Lancet*, October 10, 1903), with an excellent picture of the ophthalmoscopic appearance of the retina. (2) Gamgee, "Physiological Chemistry of the Animal Body," vol. i., p. 170; London, 1880.

and it may even be milk-white. If the blood be allowed to stand a short time in a test-tube, the fat rises to the surface and forms a thick yellowish-white layer, the depth of which varies with the degree of lipæmia. Treatment with ether or with the specific fat stains proves it to be fat. The emulsion in the serum is so fine that no fat droplets are seen upon ordinary microscopical examination. They can only be detected with the very high power. The lipæmia varies considerably from time to time. The variations are strikingly parallel to those of the general condition of the patient. In one case I recently had under my care the lipæmia only came on when the patient was comatose. There was 4 per cent. of fat in the blood. The patient recovered from the coma under treatment, and the lipæmia simultaneously disappeared. The phenomena were repeated several times in the course of a few weeks, until the patient finally died in one of the attacks.

Attempts have been made to decide where this fat in the blood comes from. Neisser and Derlin (355) investigated the melting-point, the saponification and the iodine index in their case, and showed that the fat had the same properties as that in the chyle; they concluded that it was derived from the food. Fischer's (352) view—namely, that the fat stored up in the tissues may be the source of the fat in the blood—deserves consideration. Ebstein (356) brings forward as a third view that the plasma fat of diabetic patients with lipæmia is derived from fatty degeneration of the tissues, and perhaps of the blood itself. As a matter of fact, there is no evidence to support this.

Fat is a normal constituent of the blood. It increases in amount when the fat in the food is excessive; a temporary cloudiness of the plasma may then occur even in healthy people. Normally, not more than 1 per cent. of demonstrable fat is present in the blood. In diabetic blood much higher values obtain. In the majority of cases the average is not more than 4 to 6 per cent., but Stadelmann found 15 per cent. (357), Fischer 18·1 per cent. in the ether extract. In Fischer's case, however, there was at least 2·6 per cent. cholesterin (calculated for the blood, 0·478 per cent.), so that the blood contained 10 per cent. less water than usual (69·287 per cent., against the normal of 79·17 per cent.).

There is evidence, therefore, that the fat content of the blood of diabetics increases considerably when the food contains much fat. In the diabetic cases in question, however, the food was not particularly rich in fat. In my own cases the amount of fat in the diet was no more than usual, and it was definitely shown that the blood contained practically the same amount of fat in the early morning, before any meal was given, as it did after meals. It will be remembered that the percentage of fat in the blood may be high during starvation. In the absence of food, the greater part of the energy of the body is supplied by the combustion of fat from the tissues; under these conditions, large quantities of fat may be set free, to be carried to the active cells by the blood. In diabetes, when the power to make use of carbohydrate is completely lost, the necessity for this transportation of fat becomes greater than in simple hunger. Nevertheless, the quantity of fat which, whether from the food or from the adipose tissue, is required for the

use of the cells is far less than the quantity which healthy individuals can deal with and assimilate without any trace of lipæmia. It is impossible to explain lipæmia as dependent solely upon the relations between fat ingestion, fat requirements, and fat transportation. There must be a qualitative disturbance of metabolism at the root of it.

One hypothesis suggests itself to me; I think it also occurred to Glück, Schwarz, and Fischer. The well-known researches of Cohnstein and Michaelis (358) showed that the fat which enters the blood-stream by the thoracic duct disappears with great rapidity—faster than can be accounted for by storage in the tissues or by combustion. The fat, as quickly as it enters the blood, and probably through some action of the erythrocytes, becomes converted into a compound soluble in water. The nature of this compound is uncertain; it may be one with lecithin. The phenomenon is termed "lipolysis," and the hypothetical ferment is called "lipase." The transformation of the fat into this compound soluble in water seems to be an essential stage before its entry into the cells [Pflüger (359)]. Inside the cells it becomes neutral fat again. Fischer and Schwarz suggest that in certain conditions of diabetes this lipolytic ferment is insufficient in amount, or debilitated, so that, according to the law of reversibility of ferments, its converse action preponderates. Fischer mixed normal blood with lipæmic blood in a flask, and the mixture developed lipolytic activity; the fat diminished, which was not the case when lipæmic blood alone was left *in vitro*. Fischer reminds us that, as Hanriot (360) demonstrated, the presence of the products of fat fermentation, and particularly the fatty acids, strongly inhibit lipolysis. Diabetic acidosis may thus favour the occurrence of lipæmia; but it can only be regarded as one factor amongst many, as is proved by the common occurrence of cases of extreme acidosis without lipæmia.

These explanations, which Schwarz and Fischer gave independently, are very fascinating, but there is more yet to discover. The above discussion will serve to indicate the directions in which future researches may be made upon this peculiar and hitherto obscure phenomenon.[1]

Hale White records the case of a diabetic whose blood contained a white substance soluble in alkalis, insoluble in water and salines. It was probably a proteid precipitated by the presence of a fatty substance, the fatty substance being apparently an ester of cholesterin with a high fatty acid. The "lipæmia" was thus not due to fat. The lipæmia disappeared as the patient improved. It had no relation to the diet.

8. Staining Reactions of the Blood.

If normal blood is mixed with dilute methylene blue in slightly alkaline solution, the fluid assumes a blue-green colour. Williamson (361) described a reduction process by which diabetic blood rendered methylene blue yellowish red. Bremer (362) published a modification of this which is better known. Blood was smeared in a thin and even layer upon a slide; after drying and heating for ten minutes at 135° C., it was stained

[1] Wilson and Owens, *B.J.*, vol. ij., p. 20, 1906, consider that lipæmia is neither serious nor rare; it is an abnormal metabolism of tissue fat.

for a short time with 1 per cent. solution of methylene blue. Diabetic blood remains pale green ; healthy blood in a control becomes deep blue. The pale green is the positive Bremer's reaction. Many other stains have since been found which behave differently with diabetic to what they do with normal blood [Bremer, Le Goff (363)].

Williamson and Bremer both attribute the reduction of methylene blue to the action of glucose in the blood. It has been found that as little dextrose as 0·15 to 0·20 per cent. will reduce a weakly alkaline solution of methylene blue [Hartwig (364)]. There is often as much sugar as this in diabetic blood. There is therefore no reason why this sugar should not be primarily responsible for the reaction ; and all later writers agree, upon the whole, with Williamson and Bremer (365). More exact investigation of the reaction has shown that other factors also play a part in it. Diminished alkalinity of the blood favours it [Lépine and Lyonnet, Loewy, Hartwig]. This explains why the test is positive much more constantly in severe cases of diabetes associated with acidosis than in slight forms of the disease. A discovery of Loewy's is very remarkable. He centrifugalized some diabetic blood which gave a positive reaction, and washed the deposit of blood-corpuscles with isotonic salt solution until no more sugar was dissolved. The cells, freed from sugar and from plasma, would not stain with methylene blue. I have found the same on repeating the experiment. The blood-corpuscles of a healthy man stained readily after subjection to precisely the same treatment. Either the diabetic erythrocytes still contained much sugar, which is improbable, or else the stroma or the hæmoglobin had undergone some obscure change which prevented their taking up the aniline dye. The question badly needs further investigation.

The fact that something more than the presence of sugar is at the root of the staining reactions of diabetic blood explains the inconstancy of the test in clinical medicine. Strauss (365) drew attention to this. A positive Bremer's reaction is by no means the constant phenomenon in diabetes that Williamson and Bremer supposed. It often bore no quantitative relation to the intensity of the glycosuria. The reaction was often still positive after restriction of the carbohydrate in the food had reduced the glycosuria to zero. A short while since I saw a diabetic patient again who six years before had had 0·2 per cent. of glycosuria and a very strong Bremer's blood reaction ; he now had 6 per cent. of sugar in his urine, but his blood stained extremely well with methylene blue. There are obviously several different factors at work, waxing and waning in their influence at different times. There are no quantitative comparisons to hand in which the percentage of sugar and the staining power of the blood have been accurately and simultaneously determined. Research upon this point would assist in settling the question under discussion.

9. Gases of the Blood in Diabetes.

Kraus, confirming Minkowski, found the CO_2 content of the blood to be constantly low in cases of diabetic coma, averaging 15 volumes per cent. instead of a normal 40 to 50 volumes per cent. Beddard, Pembrey, and

Spriggs (351A) examined a number of cases of diabetes, and found that in diabetic coma the quantity of CO_2 which could be extracted from the blood was half, or less than half, the normal. In the blood of non-comatose patients there was less CO_2 than in normal blood, but more than in coma. After the administration of alkalis, the amount of CO_2 present in the blood was increased.

The theory has been advanced that in diabetic coma the blood is unable, owing to its diminished alkalinity, to take up the normal amount of CO_2. Beddard, Pembrey, and Spriggs, from their experiments upon the tension of the blood in diabetes, consider that the respiratory symptoms in diabetic coma are not entirely to be explained by the assumption of a chemical disability of the blood to combine with CO_2. It seems more probable that the cells, including those of the respiratory centre, are unable to carry on the usual oxidative processes, and are in a state of oxygen starvation, although there is a sufficiency of oxygen in the blood.

VIII.—THE DIGESTIVE ORGANS.

A.—THE SALIVA.

1. Ferments—Sulphocyanide Reaction.

The diabetic patient usually has a dry mouth and little saliva ; the latter is said to be deficient in ferments [Jawein, Robertson (366)]. I do not think this really is so as a rule ; I have often found the amylolytic power of the saliva to be normal even in the worst cases. There are many exceptions in regard to its quantity also. In many diabetics the secretion is normal, and in some there is even ptyalism.

I have several times found no sulphocyanide reaction, though in most of the patients it is present, and as marked as normal.

2. Sugar.

Most researches upon the presence of sugar in the saliva have proved negative. Külz (367), however, quotes several observers who found it ; and Fleckseder (368) has recently reported two cases with a positive sugar reaction. F. Kraus, jun., working in my laboratory, and using the most sensitive tests, including that of phenylhydrazine in each case, could find no trace of sugar in the saliva of ten severe cases who were excreting sugar in large quantities. Theoretically, one would think sugar ought to appear in the saliva sometimes, seeing that a dog's salivary glands let sugar through when 0·8 per cent. is present in the blood [Weyert (369)]. Sugar values as high as this were obtained by transfusion with dextrose solution ; they scarcely ever occur spontaneously in diabetes, but one would think patients would be found now and then whose salivary glands were abnormally permeable to sugar. In all researches upon the subject it is necessary to analyze the saliva fresh and pure, since reducing bodies may be derived from the decomposition of mucin. The sweet taste in the mouth that diabetic patients often complain of is probably not due to the presence of sugar, but to that of acetone.

3. Acetone.

Acetone may occur in the saliva in simple inanition [Schuman-Leclerq, 20 to 25 milligrammes in 100 c.c. of saliva (370)]. It is a regular constituent in diabetic acidosis. The largest quantity which Kraus found in cases in my wards was 3·9 milligrammes of bodies that produced iodoform in 100 c.c. of saliva ; the patient died of coma three weeks later. The majority of our figures lay between 1·5 and 3 milligrammes. Flechseder (368) found acetone, but never aceto-acetic acid. We gave pilocarpine to one patient suffering from severe diabetes with acidosis ; 150 grammes of the saliva was examined for β-oxybutyric acid by the a-crotonic acid method, and we could detect none. The small quantities of acetone which have been found in the gastric contents in the acidosis of inanition and of diabetes are probably not entirely derived from swallowed saliva, but are—in part, at least—secreted in the stomach (371). I recovered 55 and 67 milligrammes respectively from the gastric contents of two diabetic patients who had lavage of the stomach just before coma. No alcohol had been given for some days previously. The figures are too high to be due to swallowed saliva. Acetone also occurs in the fæces, but the quantities are so small that they may be neglected in experiments upon the acetone balance [Geelmuyden, Schwarz (372)]. The fæces contain less acid per cent. than do diabetic viscera (373).

4. Reaction.

Lehmann (374) was the first to record the fact that the saliva in diabetes may be acid. He demonstrated lactic acid in the fresh saliva. Later observers have failed to find this acid [Limpricht (375)], but the acid reaction has often been confirmed. I have frequently found the mixed saliva to be acid when there has been no food in the mouth. This is not peculiar to diabetes ; it has often been noticed in health [Sticker (376)], and it may be due to bacterial and fermentative changes. In several severe cases of diabetes Mosler found the saliva acid even when obtained direct from Stenson's duct. We do not know whether the secretion is often acid whilst still within the ducts, or if it depends upon diminished alkalinity of the blood, as Kühne thinks likely, or whether the acid reaction is a bad, the alkaline a good, prognostic sign [Sticker (378)]. The facts we know at present have been discovered by casual observation, and no systematic research has been carried out upon the matter.

B.—THE FUNCTIONS OF THE STOMACH.

1. The Appetite.

Increased appetite is a very common symptom in diabetes so long as the carbohydrates are not restricted. It reflects the needs of the tissues, which are starving although permeated by juices abounding in sugar.

Thirst is also extreme ; the sugar carries much water with it into the urine ; the blood and lymph become partially dehydrated, and this has to be remedied by drinking.

The fact that diabetic patients consume so much food affords a measure of the activity of their gastric juice.

2. Motility.

The motility of the stomach is, as a rule, good. I can completely confirm Honigmann's (379) experiences. In both mild and severe cases we have had occasion to wash out the stomach for one reason or another, and we have found that the contents have been passed on at the usual rate. Fauconnet (380) nearly always found the motility normal or increased.

The above holds good for uncomplicated cases. Naturally, it is possible for diabetics to have affections of the stomach, but clinically the polyphagia and polydipsia do not seem to predispose to them. The conditions are different in the last stages of diabetes—that is to say, when the patient is debilitated and coma threatens. The gastric motility is then often much diminished ; one finds atony with stagnation, with consequent fermentations, hyperæsthesia of the mucosa, waterbrash, feelings of discomfort, vomiting, and serious loss of appetite.

3. Hydrochloric Acid.

The hydrochloric acid has been investigated by Riegel, Rosenstein, Krause, Honigmann, Gans, and Fauconnet (381) ; and there are many other observations upon it scattered through the literature [von Noorden (382)]. It shows no peculiarity in its behaviour. In quantity, it is sometimes high, sometimes low, but the variations are within the limits found in health. Acidosis has no typical effect upon it. Only in the late stages of diabetes is the hydrochloric acid obviously affected, and then it may be either completely absent or present in excess. In two patients, shortly before the onset of coma, I found 0·4 per cent. of hydrochloric acid after a test breakfast. One of these cases was known to have had the normal amount of acid a few weeks before ; both had been taking 35 to 40 grammes of sodium bicarbonate per diem for a long time in small doses.

C.—THE FUNCTIONS OF THE INTESTINE.

1. The Resorption of Food.

In most diabetic patients food resorption is good. Traube, Külz, Block (383), and others, made occasional analyses of the fæces long ago. Since then a large number of papers upon metabolism in diabetes have

been published containing careful quantitative analyses af the fæces. In uncomplicated cases the absorption of nitrogen and that of fat were normal (384).

In the course of experiments great demands have often been made upon the resorptive power of the intestine, and these have been well responded to [Lüthje]. There is no object in giving the figures here, because they were perfectly normal. Carbohydrates, particularly sugar, have often been sought for in the fæces, but have only been found in the normal small amounts. Rössler (385), giving a diet free from carbohydrate, found 0·068 and 0·078 per cent. in the fæces. After giving 100 grammes of grape-sugar, he found 0·357 and 0·415 per cent. There were no pentoses. Figures that are high usually result from diarrhœa. When the latter does not occur, the administration of even huge quantities of soluble carbohydrate does not lead to the presence of more than the normal quantity of reducing substance in the dejecta. With the " oat cure " we have not found more than 1 to 2 grammes of sugar in the fæces, even after boiling with hydrochloric acid, though 300 grammes of oatmeal were given by the mouth per diem. Lipetz's (396) cases seem to have shown no increase of carbohydrate in the fæces either. Mossé (211) records the same after potatoes.

Hirschfeld (384) drew attention to the fact, already hinted at by older observations here and there, that there are a few exceptional cases of diabetes in whom as much as 30 per cent. of the nitrogen and fat pass through the intestine when the diet is liberal but not excessive. The carbohydrate was well absorbed even in these. In five series of observations the average intake was 436·4 grammes dry weight, 34·4 grammes of nitrogen, 160·6 grammes af fat. The fæces contained 35·2 grammes of dry residue, 31·8 per cent. of the nitrogen, 34·8 per cent. of the fat. It seems likely that, in addition to the specific affection of the pancreas, the various juices of the alimentary tract were out of order in these cases. Several cases of this kind have since been carefully studied and recorded (386). The most characteristic feature was the steatorrhœa,[1] which may be so extreme that undigested fluid fat may run out *per anum* when fat is given abundantly by the mouth. The copious ash-coloured fæces are covered with an oily layer which, when it cools, bears a remarkable resemblance to butter. The high nitrogen figures, which never failed, can naturally be proved only by analysis. Minkowski and M. Abelmann (387) met with a similar phenomenon in dogs after extirpation of the pancreas. They found considerable improvement in resorption when pancreas was given with the food, a point which may be of considerable therapeutic value. Raw pancreas has proved to be of practical service in checking steatorrhœa [von Noorden, Schild and Masuyama (388)]. Pancreon and pancreatin are equally effective, as Salomon (386) showed and Sigel (214) confirmed. The table on p. 624 gives the results of analyses in one case of Salomon's in which pancreatin was administered.

[1] Weintraud is of the opinion that the steatorrhœa of defective pancreatic secretion may be distinguished from that of catarrh, amyloid degeneration, etc., of the intestine by the fact that the former is accompanied by marked azotorrhœa, whilst in the latter the nitrogen resorption is good. Our own experience is not the same as Weintraud's; we have often seen azotorrhœa in intestinal affections.

	Recovered from the Fæces—	
	Nitrogen.	Fat.
	Per Cent.	Per Cent.
Without treatment	22·8	53·3
With pancreatin, 0·25 gramme five times a day..	9·2	17·3

I will not go into these interesting disorders of resorption in any further detail. They do not concern diabetes mellitus proper, but only its complications. The cases are rare. I have treated about 2,000 diabetic patients, and have found only twelve marked cases of steatorrhœa amongst them. I refer the reader to the chapter upon Affections of the Pancreas.

2. Decomposition in the Intestine.

A discussion of great theoretical importance has lately centred around the excretion of aromatic products of putrefaction in diabetic urine. Blumenthal, and his pupils Rosenfeld and Lewin (389), resuscitated an old idea, and believed they were able to prove that aromatic radicles, particularly indol, become free in the tissues during protein katabolism, and that they combined with sulphuric or glycuronic acid esters and thus appeared in the urine. They claimed that the aromatic constituents of the urine arose in this way in inanition (see Vol. I.), experimental phloridzin glycosuria, and diabetes mellitus. Carletti, Reale, Gilbert and Weil, and Moraczewski (390) incline to this view. Ellinger, Mayer, and Jaffé (391) oppose it, and we think rightly. Their careful researches make it impossible to believe that the aromatic constituents of the urine have any other origin than bacterial destruction of protein. In uncomplicated diabetes bacterial putrefaction of nitrogenous substances occurs only in the bowel, and we cannot but call the resultant bodies in the urine enterogenous. Their quantity affords a reliable measure of the putrefaction that is taking place in the intestine (see Vol. I.).

The peculiar conditions of diabetic diet, its richness in protein and poorness in carbohydrate, are factors which we know from physiology (Vol. I.) are the most favourable for increasing the aromatic bodies in the urine. We have actual records that this is so (392). My own experience is that the excretion of ethyl-sulphuric acids, which are only part of the enterogenous products of putrefaction, bears a rather close relation to the peculiarities of diabetic diet. This is also true of the indican reaction, and holds good both of mild and of severe uncomplicated cases. Leo (393) expresses the same opinion. Moraczewski's (392) numerous figures for indican and for ethyl-sulphuric acids are practically normal, although on occasional days they may have been abnormally high.

In fifteen diabetic patients without complications, but all with severe glycosuria, we found the following results when the diet was restricted

until the most favourable conditions of resorption and excretion had been reached :

		Gm.	
Nine times	.. .. ..	0·1 –0·2	Aromatic sulphates.
Five times	.. .. ..	0·2 –0·25	,,
Twice	.. .. ..	0·30–0·35	,,

The figures are the average for periods of from three to four days. In the last two cases only could the excretion be termed increased. In the stage of coma, and just before it, we found 0·18 and 0·24 gramme per diem three times. There was no increase. Strauss and Philippsohn (392) found the same. I will just give an abstract of the determinations made by Herter and Wakeman in my laboratory in the winter of 1903-1904 (see table, p. 626). It will be seen that there are one or two cases which show increased excretion of enterogenous products of decomposition. Such cases occur in every disease. There is no reason for giving them any special significance in diabetes. The cases in which the figures were normal are far too numerous for the others to be more than the usual exceptions.

Herter and Wakeman also estimated the quantities of phenol. Strasser (394) is the only other observer hitherto who has published a research covering the field so widely. He found the phenol constantly increased up to 0·69 gramme per diem. Neuberg (395) has shown, however, that the method used by Strasser always gives too high a figure in the presence of carbohydrate.

Lipetz (396), using the Schmidt-Strasburger method, came to the conclusion that the number of bacteria in the fæces is much augmented when a person is upon oatmeal diet. This is an interesting point, but it does not explain, as Lipetz believes it does, the decrease in glycosuria and acetonuria that usually follows the adoption of von Noorden's " oat cure "—250 to 300 grammes of oatmeal per diem. The proportion of the oatmeal that undergoes fermentation and escapes absorption must be a very small part of the whole. The resorption takes place mainly in the small intestine, whilst the bacterial decomposition is restricted to the large. Were it not so, the symptoms of infection of the ileum and jejunum would not be entirely absent.

The question of decomposition in the bowel has thus a great importance in diabetes, because not only the onset of coma [Schmitz (397)], but also the disease as a whole, has been referred to its effects and influence. De Dominicis, and later G. Töpfer (398), extracted the fæces of diabetics either by maceration or by dialysis, and by administering the extract partly by the mouth, partly subcutaneously, they maintained that they had produced glycosuria in animals. Lépine and Leo (399) repeated the experiments, but with negative results. The discussions on these experiments have been forgotten, but they might serve as starting-points for fresh researches.

Name.	*Age (Years).*	*Nitrogen.*	*Sugar.*	*Acetone.*	*Oxy-butyric Acid.*	*NH_3.*	*Volatile Fatty Acids (Deci-normal NaOH).*	*Aromatic Oxy-acids, including Hippuric Acid.*	*Phenol.*	*Ethereal Sulphates.*	*Length of Experiment.*	*Diet.*
		Gm.	Gm.	Gm.	Gm.	Gm.	C.c.	Gm.	Gm.	Gm.	Days.	
Herr K.	60	—	38·5	0·347	—	1·48	185·0[1]	0·410	—	0·213	3	Ordinary.
		—	32·0	0·494	—	2·11	216·0	0·371	—	0·221	3	Vegetable day.
		—	31·9	1·286	—	2·09	247·0	0·519	—	0·206	3	Ordinary.
Frau Pl.	40	5·5	104·0	1·61	—	1·12	188·0	2·113	—	0·235	3	250 grammes oatmeal, 100 grammes rice protein, 300 grammes butter.
Child R.	5	7·8	7·3	0·15	—	0·49	79·4	0·119	—	0·073	3	Ordinary+400 c.c. milk+30 grammes oats.
		—	3·1	0·65	—	1·11	55·6	0·518	0·320	0·38	8	Ordinary+80 grammes cream.
		3·7	6·0	0·14	—	0·74	20·3	0·222	0·316	0·11	3	150 grammes oats + 200 grammes butter.
		1·6	3·2	0·0	—	0·40	13·2	0·186	0·170	0·085	3	150 grammes oats+50 grammes rice protein.
		4·7	17·2	0·0	—	0·55	10·4	0·401	0·140	0·103	3	150 grammes oats; eggs instead of rice protein.
		7·8	0·0	0·75	—	1·01	9·1	—	0·280	0·120	2	Vegetable day.
Herr W.	30	25·6	322·0	5·71	—	6·4	325·0	1·30	—	0·408	3	Ordinary+150 grammes potatoes+75 grammes bread.
		22·6	247·0	11·11	123·3	7·1	302·0	2·83	—	0·407	5	150 to 250 grammes oatmeal, butter, Roborat, 100 to 150 grammes lævulose, 50 to 100 grammes sodium bicarbonate.
		20·0	254·0	10·70	174·6	6·8	319·0	1·28	—	0·261	5	750 to 1,500 grammes potatoes, butter, Roborat, eggs, 50 to 100 grammes lævulose. 40 to 60 grammes sodium bicarbonate.
		22·1	150·0	8·20	121·3	6·2	232·0	1·36	0·79	0·273	5	+ 200 grammes meat daily.

[1] The numbers denote the number of c.c. of decinormal NaOH necessary for the saturation of the daily quantity of volatile acids.

LITERATURE.

Sugar present in the Blood.

1. Pickardt: Nachweis von Traubenzucker im Blut. Z. p. C. **17.** 217. 1893.—Miura: Kommt im Blut Traubenzucker vor? Z. B. **32.** 279. 1895.—Hanriot: Sur la nature du sucre du sang. C. r. S. B. 14 Mai, **1898.**

2. Pavy and Siau: On the Nature of the Sugar Present in Normal Blood, Urine, and Muscle. J. P. **26.** 282. 1901.

2a. Embden: Ueber Zuckerbild. bei künstlicher Durchblutung der glykogenfreien Leber. Be. P. P. **6.** 44. 1905.

3. Drechsel: Ueber einen neuen S- und P-haltigen Bestandteil der Leber. J. p. C. **33.** 425. 1886.

4. Baldi: Ueber die Verbreitung des Jekorins im tier. Organismus. D. A. **1887.** Suppl. 100.—Jacobsen: Ueber die in Aether löslichen reduzierenden Substanzen des Blutes. Sk. Ar. P. **6.** 262. 1895.—Henriques: Ueber die reduzierenden Stoffe des Blutes. Z. p. C. **23.** 244. 1897.—Bing: Ueber das Jekorin. C. P. **1898.** 209.—Bing: Über die reduzierenden Substanzen im Blute. Sk. Ar. P. **9.** 336. 1899.

5. Kolisch and Stejskal: Ueber den Zuckergeh. des normalen und diabet. Blutes. W. k. W. **1897.** 1101.

6. Kolisch and Stejskal: Ueber den Zuckergehalt des normalen und diabet. Blutes. W. k. W. **1898.** 135.

Renal Diabetes.

7. v. Mering: Ueber den exper. Diab. V. C. M. **1886.** 185.

8. Naunyn: Der Diab. mell. 1898. Pp. 106, 175; and v. Noorden: Die Zuckerkrankheit. P. 91.

9. Achard and Weil: Imperméabilité rénale et hyperglycémie dans le diab. S. m. H. 21 Jan. **1898.**

10. Lépine: Hyperglycémie extraordinaire chez une femme diab. avec lésions rénales. Re. M. **1897.** 832 (in blood, 1·06 per cent. sugar; urine not estimated).

11. Schupfer: Dell' influenza di alcuni stati morb. sull' audamento del diab. Bu. R. **24.** 1897-98.—Schupfer: L'albuminuria nel diab. ed il diab. renale. P. **1900.** 1 and 81.

12. Richter: Zur Frage des Nierendiab. D. m. W. **1899.** No. 51; and über die Beziehungen zwischen Nieren und Glykosurie. Z. M. **41.** 160. 1900.—Ellinger and Seelig: Einfl. von Nierenveränderungen auf den Verlauf des Pankreasdiab. Festschr. f. Jaffé. P. 349. 1901.

13. Jacobi: Ueber künstlichen Nierendiab. E. A. **35.** 213. 1895.

14. Neumann: Glykosurie bei einem Herzfehlerkranken. E. A. **36.** 72. 1895.

15. Strauss: Zur Lehre von der neurogenen und thyreogenen Glykosurie. D. m. W. **1897.** Nos. 18 and 20.

16. Richter: Diuretika und Glykosurie. Z. M. **35.** 463. 1898.

17. Richter: l. c. (12).—Kossa: Ueber Chromsäurediab. Ar. P. M. **88.** 627. 1902.—Rose: Der Blutzuckergehalt des Kaninchenharns. E. A. **50.** 15. 1903.—Schilling: Prüfung der Nierenfunktion nach Nephrektomie. E. A. **52.** 140. 1904.

18. Naunyn: l. c. (8). P. 107.

19. Klemperer: Ueber regulat. Glykosurie und renalen Diab. V. i. M. 18 Mai, **1896.**—Kolisch and Buber: Zur Kasuistik des Diab. decipiens. W. k. W. **1897.** 553.—Lüthje: Beitr. zur Frage des renalen Diab. Mü. m. W. **1901.** No. 38.

20. Lépine: Nécessité d'admettre l'intervention d'un élément rénale dans le Diab. sucré. Co. M. 14 Août, **1895,** and Re. M. **1896.** 594.

21. Ueber "Nierendiabetes," also Marcuse: Gibt es einen klinischen renalen Diab.? A. C. Z. **1896.** No. 49.—Lépine: Réc. trav. sur la pathogénie des Diab. Re. M. **1896.** 594.—Lang: Ueber Glykosurie als Initialsymptom einer Schrumpfniere. Medizin. Woche. **1902.** 17 Nov.—Lépine: Sur diabète rénale. B. k. W. **1905.** Ewald-Festschr. P. 20.

Diabetic Hyperglycæmia.

22. Bernard: Über Diabetes. **1878.** 75.

23. Pavy: The Physiol. of the Carbohydrates. 1894.—Seegen: Die Zuckerbild. im Tierkörper. 1900.—Seegen: Der Diabetes mellitus. 1893.—Seegen: Stud. über Stoffwech. 1887.—Naunyn: l. c. (8). P. 170.

24. Frerichs: Ueber den Diabetes. 1884. P. 270.

25. v. Mering u. Minkowski: Diab. mell. nach Pankreasexstirpation. E. A. **26.** 371. 1890.—Minkowski: Über Diab. mell. nach Pankreasexstirpation. B. k. W. **1892.** No. 5.

26. Lépine: Sur l'hyperglycémie et la glycosurie comparées, conséc. à l'ablation du pancréas. Se. m. **1895.** 434.

27. Pavy: l. c. (23). P. 193.

28. Seegen: Die Zuckerbild. im Tierkörper. P. 269. 1900.

29. Lépine: Rélations entre la glycémie et la glycosurie. C. r. S. B. 1 Déc., 1900.

30. Schlesinger: Ueber einige ursächliche Bedingungen für das Zustandekommen der alimentären Glykosurie. W. k. W. **1902.** No. 30.

Hepatogenous Hyperglycæmia.

31. Pflüger: Glykogen. Ar. P. M. **96.** 303 ff. 1903.

32. Bock and Hoffmann: Experimentalstud. über Diab. 1874.—Butte: Action du nerf pneumogastrique sur la fonction glycogénique du foie. C. r. S. B. 17 Fév., 1894.—Levene: Die zuckerbildende Funktion des N. vagus. C. P. **8.** 337. 1894.—Cavazzani: Sur la fonction glycogénique du foie. Ar. i. B. **21.** 447. 1894.

33. Luchsinger: Phys. und Pathol. des Glykogens. Diss. Zurich, 1875.

34. See Frerichs: l. c. (24); Naunyn (8); Pflüger (31).

35. Straub: Ueber die Bedingungen des Auftretens der Glykosurie nach Kohlenoxydvergiftung. E. A. **38.** 139. 1896.—Rosenstein: Einfl. der Nahrung auf die Zuckerausscheid. beim Kohlenoxyd-Diab. Diss. Ber. 1897.—Seelig: Ueber Aetherglykosurie. E. A. **52.** 481. 1905.

36. Frerichs: l. c. (24).—Naunyn, v. Noorden (8).—Pflüger (50a). P. 399 ff. —Williamson: Diabetes. 1898. Pavy: Croon Lectures, 1878, 1894, etc.

37. v. Noorden: l. c. (8). P. 20.—Diabetes Mellitus, its Patholog. Chem. and Treatment. P. 148. 1905.

37a. v. Noorden: Lit. No. 8. P. 20.

38. Eckhard: B. A. P. **8.** 77. 1879.

38a. Pflüger: l. c. (31). P. 391 ff.

39. Hoffmann: Zur Path. u. Ther. des Diabetes. V. C. M. P. 159. 1896.

Alimentary Glycosuria.

40. Hofmeister: Ueber die Assimilationsgrenze der Zuckerarten. E. A. **25.** 240. 1889.

41. Strauss: Cf. H. Sachs: Ueber das Verhalt. der Lävulose im Stoffwech. 1900.

41a. Wille: Die aliment. Glykosurie und ihre Beziehungen zu Pankreasaffektionen. D. Ar. M. **63.** 546. 1899.

42. Lorand: Les rapp. du pancréas avec la thyréoide. C. r. S. B. 1904. 25 Mars.—Die Entstehung der Zuckerkrankh. und ihre Beziehungen zu den Veränderungen der Blutgefässdrüsen. 1903.

43. Klippel et Lefas: Le pancréas dans les cirrhoses rein du foie. Re. m. **1903.**—Steinhaus: Ueber das Pankreas bei Leberzirrhose. D. Ar. M. **74.** 537. 1902.

44. Bleichröder: Ueber Leberzirrhose und Blutkrankh. Ar. p. A. **177.** 435. 1904.

45. Hoppe-Seyler: Ueber Veränderungen des Pankreas bei Arteriosklerose. XXI. V. C. M. 130. **1904**; and D. Ar. M. **81.** 119. 1904. — Herxheimer: Ueber Pankreaszirrhose bei Diabetes. Ar. p. A. **183.** 228. 1906.

46. Poll: Ueber aliment. Glykosurie bei fieberhaften Infektionskrankh. A. K. (Festschr.) **1896.** 59. and F. M. **1896.** 501.

47. Strauss: Über alimentäre "spontane" und diabet. Glykosurien. Z. M. **39.** 202. 1900.

Glycogen in the Tissues.

48. Frerichs: l. c. (24).—Külz: Zur Kenntnis des menschl. Leberglykogens. Ar. p. M. **13.** 267. 1876.—v. Mering: Zur Glykogenbild. in der Leber. Ibid. **14.** 284. 1877.—Sandmeyer: Untersuch. u. Demonstrationen. X^th V. C. M. **1891.** 341.

49. Naunyn: l. c. (8). P. 157.

50. Frerichs: l. c. (24). P. 272.

50a. Pflüger: Das Glykogen u. seine Beziehungen zur Zuckerkrankh. 496. 1905.

51. Hédon: Sur la pathog. du diab. conséc. à l'exstirp. du pancréas. Ar. P. **1892.**—Minkowski: Über Diab. mell. 1893. P. 77.—Sandmeyer: Ueber die Folgen der partiellen Pankreas-exstirp. beim Hunde. Z. B. **31.** 12. 1894.—Kausch: Ueber den Diab. mell. der Vögel nach Pankreasexstirp. E. A. **37.** 274. 1896.—Embden and Almagia: Ueber die Zuckerausscheid. pankreasloser Hunde nach Alanindarreichung. Be. P. P. **7.** 298. 1905.

52. Pflüger: Glykogen. Ar. P. M. **96.** 366. 1903.

53. De Dominicis: Ueber Diabetes pankreatic. Mu. m .W. **1891.** Nr. 41, 42. —Minkowski: Ueber den Diab. mell. nach Exstirpation des Pankreas. 1893. P. 77.

54. Ehrlich and Frerichs: Ueber das Vorkommen von Glykogen im diabet. u. normalen Organismus. Z. M. **6.** 33. 1883.—Straus: Contrib. à l'étude des lésions histol. du rein dans le diab. sucré. Ar. P. **6.** 322. 1885, et **10.** 76. 1887.—Ebstein: Ueber Drüsenepithelnekrose beim Diab. mell. Ar. M. **28.** 143. 1881; und Weiteres über Diab. mell. Ibid. **30.** 1. 1882.—Ferrari: Sur les altérations des organes dans le diab. sucré. Ar. i. B. **4.** 145. 1883.—Marthen: Ueber die Gieson'sche Färbung bei Diabetesnieren. Ar. p. A. **138.** 556. 1894.

55. Kühne: Ueber das Vorkommen zuckerbild. Substanzen in pathol. Neubildungen. Ar. p. A. **32.** 536. 1865.—Ehrlich: Lit. No. 54. P. 40.

56. Gabritschewsky: Mikrosk. Untersuch. über Glykogenreaktion im Blute. E. A. **28.** 272. 1891.—Minkowski: l. c. (53). P. 100.—Hirschberg: Ueber die Jodreaktion des Blutes. Z. M. **54.** 223. 1904.

57. Leube: Ueber Glykogen im Harn des Diabetikers. Ar. p. A. **113.** 391. 1888.

58. v. Noorden: l. c. (8). P. 85.

Deficient Sugar Consumption.

59. Lépine et Barral: De la glycolyse du sang circulant dans les tissus vivants. C. r. méd. 20. VII. **1891.**

60. Chauveau et Kaufmann: Sur la pathog. du diabète. C. r. S. B. **45.** 17. 1893.

61. Seegen: Die Zuckerbild. im Tierkörper. 1890.

62. Naunyn: l. c. (8). P. 415.

62a. v. Noorden: Die Zuckerkrankh. und ihre Behandlung. P. 10. 1895.—Lehrb. der Pathol. des Stoffw. P. 85. 1893.

63. Külz: Beitr. zur Pathol. und Ther. des Diabetes. P. 130. 1874.

64. Bunge: Physiol. Chemie. P. 377. 1889.

65. Minkowski: l. c. (51). P. 80.

66. Voit: Ueber die Glykogenbild. nach Aufnahme verschiedener Zuckerarten. Z. B. **28.** 258. 1892.

67. Lüthje: Zur Frage der Zuckerbild. im tier. Organismus. Mü. m. W. **1902.** Nr. 39.—Die Zuckerbild. aus Glyzerin. D. Ar. M. **80.** 98. 1904.

67a. v. Noorden: Lit. Nr. 68. P. 85 (1893).

68. v. Noorden: Pathol. des Stoffwech. P. 399. 1893.—v. Noorden: Die Zuckerkrankheit. P. 54. 1901.

69. v. Leube: Ueber Stoffwechselstörungen und ihre Bekämpfung. P. 19. 1896.—Krehl: Patholog. Physiol. P. 423. 1904.—Pflüger: Lit. No. 50a. P. 447.

Overproduction of Sugar.

70. Naunyn: l. c. (8). P. 426.

80. Rosenfeld: Ueber Fettbild. aus Kohlenhydraten. 76. V. N. A. (Abt. inn. Med. V. Sitz.). **1904.**

81. Külz: Beitr. zur Pathol. u. Ther. des Diabetes. **2.** 181. 1875.—Cremer: Entsteht aus Glyzerin und Fett im Körper Traubenzucker? Mü. m. W. **1902.** 944.—Lüthje: l. c. (67).

82. Lüthje: l. c. (67). 1902.—Mohr: Ueber die Zuckerbild. im. Diab. mell. Z. M. 52. 337. 1904 (on Lecithin cf. p. 353).

Formation of Sugar from Albumin.

83. Naunyn: Ueber Diab. mell. E. Ar. **3.** 93. 1875.—v. Mering: Zur Glykogenbild. in der Leber. Ar. P. M. **14.** 281. 1876.—Külz: Beitr. zur Kenntniss des Glykogens. Marburger Festschr. f. Ludwig. P. 69. 1890.

84. Cremer: Physiol. des Glykogens. Er. Ph. **1.** 803. 1902. (Biochemie).

85. Pflüger: Bedeutung der neuesten Arbeiten über den Pankreasdiabetes. Ar. P. M. **106.** 168. 1904.

85a. Lüthje: Zur Frage der Zuckerbild. aus Eiweiss. Ar. P. M. **106.** 160. 1904.—Pflüger: Lit. No. 50a. P. 303.

86. Pflüger: l. c. (31). P. 279.

87. Kossel and Neumann: Beitr. zur Physiol. der Kohlenhydrate. D. A. **1894.** 536.—Pavy: The Physiol. of the Carbohydrates. 1894.—Müller and Seemann: Die Abspaltung von Zucker aus Eiweiss. D. m. W. **1899.** 209.—Krawkow: Ueber die Kohlenhydratgruppe im Eiweissmolekül. Ar. P. M. **65.** 281. 1896.—Blumenthal: Ueber den Stand der Frage der Zuckerbild. aus Eiweisskörpern. D. m. W. **1899.** Nr. 49 and 50; Ueber Kohlenhydrate in den Eiweissverbindungen. Z. M. **34.** 166. 1898.—Langstein: Die Kohlenhydratgruppe des kristallisierten Ovalbumins. Z. p. C. **31.** 49. 1900; Die Kohlenhydrate der Eiweisskörper des Blutserums. Mü. m. W. **1902.** Nr. 45.

88. Langstein: Die Kohlenhydratbild. aus Eiweiss. Er. Ph. (Biochemie). **1.** 63. 1902, and **3.** 453. 1904.

89. Lüthje: Stoffwechselvers. an einem Diabetiker. Z. M. **39.** 397. 1900.—Falta: Einige Fragen betr. den Eiweiss-stoffwechsel bei Diab. mell. V. C. M. XXI. **1904.** 496.—Therman: Zuckerausscheid. im Diab. mell. Sk. Ar. P. **17.** 1. 1905.—v. Noorden: Path. und Ther. des Diab. mell. D. m. Z. **1902.** No. 22.—Mohr: l. c. (82).

90. Cohn: Zuckerbild. aus Eiweiss. Z. p. C. **28.** 211. 1899.—Müller: Mucins. Z. B. **42.** 468. 1901.

91. Cohn: l. c. (90).—Simon: Zur Physiol. der Glykogenbild. Z. p. C. **35.** 315. 1902.—Halsey: Ueber Phloridzin-Diabetes bei Hunden. Sit. M. 17 Mai, 1899.—Kraus: Ueber Zuckerbild. aus Eiweiss. B. k. W. **1904.** P. 7.

92. Mohr: l. c. (82). P. 350.—Neuberg and Langstein: Ein Fall von Desamidierung im Tierkörper. Eng. Ar. **1903.** 514.—Kraus: l. c. (91).—Embden and Salomon: Ueber Alaninfütterungsvers. am pankreaslosen Hunde. Be. P. P. **5.** 507. 1904, and **6.** 63. 1904.—Hirsch: Ueber das Verhalt. der Monaminosäuren im hungernden Organismus. Z. e. P. **1.** 141. 1905.

93. Nebelthau: Exper. Beitr. zur Lehre von der Zuckerbild. Mü. m. W. **1902.** 917.

93a. Mohr: Ueber die Zuckerbild. aus Eiweiss. Z. e. P. **2.** 467. 1906.

94. Pflüger: Beitr. zur Frage nach dem Ursprung des im Pankreasdiab. ausgesch. Zuckers. Ar. P. M. **108.** 115. 1905.

95. Lüthje: Stoffwechselvers. an einem Diabetiker. Z. M. **39.** 397. 1900.—Kasuistisches zur Klinik und zum Stoffw. des Diabetes. Ibid. **43.** 225. 1901.—Stradomsky: Ueber den Einfl. einiger Eiweisskörper auf die Zuckerausscheid. Z. d. p. T. **4.** 282. 1902.—Schumann-Leclerq: Ueber den Einfl. des Pflanzeneiweisses auf die Zuckerausscheid. W. m. W. **1903.** 850.—Falta: Ueber einige Fragen des Eiweiss-stoffwech. V. n. G. 18 Feb., 1903, and l. c. (89).—Mohr: l. c. (82).—Therman: (89).

96. Kraus: Phloridzindiabetes und chem. Eigenart. D. m. W. **1903.** 221.

97. Abderhalden: Bergell and Dörpinghaus: Verhalt. des Körpereiweisses im Hunger. Z. p. C. **41.** 153. 1904.

97a. Pflüger: Das Fett wird als Quelle des Zuckers sichergestellt, etc. Ar. P. M. **108.** 473. 1905.

97b. Pflüger: Lit. Nr. 50a. P. 497.

98. Magnus-Levy: Ueber Zuckerbild. aus Eiweiss und das Verhalt. des resp. Quotienten im Diabetes. V. p. G. 1 März, **1904.**

99. Landergren: Über die Eiweisszersetz. des Menschen. Sk. Ar. P. **14.** 112. 1903.

100. v. Mering: Ueber Diabetes mellitus. Z. M. **16.** 431. 1889.

101. Lüthje: Ist die Zerstörung des Zuckers nach Pankreasexstirp. vollständig aufgehoben? Mü. m. W. **1902.** No. 36.

101a. Pflüger: Lit. No. 94.—Minkowski's Abwehr, etc. Ar. P. M. **110.** 1. 1905.—Minkowski's neueste Verteidigung, etc. Ibid. **111.** 61. 1906.—Minkowski: Ueber die Zuckerbild. im Organis. beim Pankreas-diabetes. Ibid. **111.** 13. 1906.

102. Lusk, Reilly, Nollan: Phloridzindiabetes in Dogs. A. J. P. **1.** 395. 1898.—Lusk: Ueber Phloridzindiabetes. Z. B. **42.** 31. 1901.—Stiles and Lusk: Action of Phloridzin. A. J. P. **10.** 1 Sept., 1903.—Kumagawa u. Hayashi: Zuckerbild. aus Fett. D. A. **1898.** 431.—Halsey: Ueber Phloridzindiab. bei Hunden. Sit. M. 1899. No. 5.—Hartogh u. Schumm: Zur Frage der Zuckerbild. aus Fett. E. A. **45.** 11. 1900.—Rumpf: Ar. P. M. **97.** 98. 1903.

Formation of Sugar from Fat.

102a. Rumpf: Eiweissumsatz und Zuckerausscheid. beim Diab. mell. B. k. W. **1899.** 185.—Rosenqvist: Zur Frage der Zuckerbild. aus Fett. B. k. W. **1899.** 612.—Mohr: Zur Frage der Zuckerbild. aus Fett. B. k. W. **1901.** 919.—Hesse: Ueber Eiweissumsatz u. Zuckerausscheid. des schweren Diabetikers. Z. M. **45.** 237. 1902. Ar. p. A. **4.** 109. 1852.

102b. Traube: Ueber die Verdauung des Fettes bei Diab. mell. Ar. p. A. **4.** 148. 1851.—Bouchardat: De la Glycosurie ou Diab. sucré. 1883.—Cantani: Diab. mell. (Deutsch). 1880.—Ebstein: Ueber die Lebensweise der Zuckerkranken. 1892.

102c. Weintraud: Ueber den Stoffw. im Diab. mell. Bib. M. DI, Heft 1. 1893.—Hirschfeld: Die Zuckerkrankheit. 1902.—Lüthje: Stoffwechselvers. an einem Diabetiker. Z. M. **39.** 397. 1900.—Schwarz: Untersuch. über Diabetes. D. Ar. M. **76.** 233. 1903.—Hübner: Hat Fett einen Einfl. auf die Zuckerausscheid. beim Diab. mell.? Z. d. p. T. **7.** 662. 1904.

102d. Lengyel: Die Eiweissentziehung als diätet. Heilmittel bei Diab. mell. U. P. **1898.** No. 41.—Mohr u. Loeb: Diab. Acidosis. C. S. **1902.** 193.

103. Loewi: Zur Frage nach der Bild. von Zucker aus Fett. E. A. **47.** 68. 1902.—Schmid: Ueber den Einfl. der Fettsäuredarreichung auf die Grösse der Zuckerausscheid. im Phloridzindiab. E. A. **53.** 429. 1905.

104. Pflüger: Ueber die im tier. Körper sich vollziehende Bild. von Zucker aus Eiweiss und Fett. Ar. P. M. **103.** 1. 1904.—Lit. Nr. 50a. P. 328.

104a. Embden, Salomon, Schmidt: Ueber Azetonbild. in der Leber. Be. P. P. 8. Hft. 3, 4. 1906.

105. Rumpf: Diabetes mellitus. Z. M. **45.** 260. 1902.—Rosenqvist, Mohr, Hesse: (102a).

106. Lusk: Ueber Phloridzindiab. Z. B. **43.** 32. 1903.—Müller: l. c. (90).—Lüthje: (102c).—Loewi: (103).—Kumagawa u. Hayashi: (102).—Hesse (Anm. 102a).—Landergren: (99).—Langstein: (88). Cf. A. J. P. Vols. 1, 3, 9, 10.

107. Mohr: l. c. (102a).—Ascoli: Sulla glucosuria diab. e la glucopoiesi da grassi. Ma. **31.** 844. 1901.

107a. Pflüger: Lit. Nr. 50a. P. 358.

108. Umber: Das Verhalt. von Zucker- und N-Ausscheid. beim Eiweisszerfall im Diab. T. G. **1901.** Okt.

109. Rubner: Gesetze des Energieverbrauchs. 385. 1902.

110. Seegen: Die Zuckerbild. im Tierkörper. 1890. 152.—Weiss: Ueber die Bild. von Zucker aus Fett im Tierkörper. Z. p. C. **24.** 542. 1898.—Bunge: Physiol. Chemie. 1901.

111. Zuntz u. Cavazzani: Ueber die Zuckerbild. in der Leber. Eng. A. **1898.** 539.—Mortuori: Sulla transformaz. dei grassi in zuchero nel fegato. Ma. **30.** 450. 1900.—Jacobi: Ueber die Oxyd.-Fermente in der Leber. Ar. p. A. **157.** 235. 1899.—Abderhalden u. Rona: Bild. von Zucker aus Fett. Z. p. C. **41.** 303. 1904.

112. Cremer: Phys. des Glykogens. Er. Ph. I. 1. 895. 1902.

113. Mandel and Lusk: Respir. Experiments in Phloridzin. A. J. P. **10.** 47. 1903.

114. Bouchard et Degrez: Sur la transform. de la graiss en glycogène. J. P. P. G. **2.** 237. 1900.

114a. v. Noorden: Modern Problems of Metabolism. A. J. M. S. **1905.** Oct.—v. Noorden u. Embden: Einige Probleme des intermed. Kohlenhydrat-Stoffwech. Ct. P. S. **1.** 1. 1906.

Pancreas Diabetes.

114b. Embden u. Salomon: Fütterungsversuche am pankreaslosen Hunde Be. P. P. **6.** 63. 1905.

115. De Dominicis: Studii sperim. intorno agli effetti delle estirpaz. del pancreas. Gi. i. S. **1889.** 801.

116. von Mering u. Minkowski: Diab. mell. nach Pankreasexstirp. C. k. M. **1889.** 393, and E. A. **26.** 371. 1889.

117. Minkowski: Diab. mell. nach Pankreasaffektion. B. k. W. **1890.** Nr. 8. —Diab. mell. nach Exstirpation des Pankreas. 1893. Störung der Pankreas-funktion als Krankheitsursache. Er. P. **1.** 69. 1896.

118. Lépine: Die Beziehungen des Diab. zu Pankreas-Erkrankungen. W. m. P. **1892.** Nr. 27-32. — Genèse des différentes formes de diab. sucré. Se. m. **1897.** 277.—Bases physiol. de l'étude pathog. du diabète. Re. m. **1900.** Pp. 595, 683, 760, 903.—Sauerbeck: Die Langerhansschen Inseln des Pankreas und ihre Beziehungen zum Diab. mell. Er. P. **8.** 2. Abt. 538. 1904.

118a. Schultz u. Zülzer: Zur Frage der Totalexstirp. des Pankreas beim Hunde. C. P. **19.** Nr. 1. 1905.—Pflüger, Minkowski: Lit. Nr. 94 and 101a. —Pflüger: Ob die Totalexstirp. des Pankreas mit Notwendigkeit Diabetes bedingt. Ar. P. M. **106.** 181. 1905.

118b. v. Noorden: Modern Problems of Metabolism. A. J. M. S. 28. Oct., 1905.

119. Kausch: Ueber den Diab. mell. der Vögel. E. A. **37.** 274. 1896; and **39.** 219. 1897.

120. Markuse: Ueber die Bedeutung der Leber für das Zustandekommen des Pankreas-diab. Z. M. **26.** 225. 1894.

121. Sandmeyer: Ueber die Folgen der partiellen Pankreasexstirp. beim Hund. Z. B. **31.** 12. 1894.

122. Minkowski: l. c. (117). — Thiroloix: Rôle de l'alimentation dans le diab. pancréatique expér. C. r. S. B. 14 Av., **1894.**—Hédon: Sur la pathog. de diab. conséc. à l'exstirp. du pancréas. Ar. P. **1892.** 245.—Lüthje: l. c. (101).

123. Minkowski: l. c. (117). **1896.**—Hédon: Greffe souscutanée du pancréas. Ar. P. **1892.** 617.—Thiroloix: Physiol. du pancréas. De la dissociation expér. des sécrétions ext. et int. de la glande. Ar. P. **1892.** 716.

124. Lorand: Cf. 42 and 145.

125. For Literature, see Naunyn: l. c. (8). P. 77.

126. Chvostek: Ueber aliment. Glykosurie bei Morbus Basedowii. W. k. W. **1892.** Nr. 17, 18, 22.

127. Zülzer: Alimentäre Glykosurie in Krankheiten. von Noorden's Beitr., etc. **2.** 46. 1894.—Strauss: Neurogene und thyreogene Glykosurie. D. m. W. **1897.** Nr. 18 and 20.—Naunyn: l. c. (8). P. 78.

128. Ewald: Schilddrüsenther. bei Myxœdem. B. k. W. **1895.** Nos. 2, 3.— v. Noorden: Zur Theorie und Praxis der Schilddrüsenther. Z. p. A. **1896.** 1.

129. Lépine: Sur la présence norm. dans la chyle d'un ferment destructeur du sucre. C. r. A. M. **110.** 742. 1890.—Sur le pouvoir glycolytique du sang et du chyle. Ibid., 23 Juin, **1890.**—Sur la glycolyse dans le sang normal et dans le diab. Ibid. **1893.** 17 Juill.—Die Beziehungen des Diabetes zu Pankreaserkrankungen. W. m. P. **1892.** Nos. 27-32.—De la glycolyse dans ces rapp. avec le diabète sucré. Se. M. **1903.** 2 Déc.

130. Arthus: Sur le ferment glycolytique. C. r. S. B. **1891.** p. 63. Glycolyse dans le sang. Ar. P. **1891.** 425. **1892.** 387.—Colenbrander: Over het verdwijnen van suiker uit het bloed. N. T. 10 Sept. **1892.**—Minkowski: Über den Diab. mell. nach Pankreasexstirpation. B. k. W. **1892.** 90.—Seegen: Die Zuckerumsätze im Blute. W. k. W. **1892.** Nr. 14, 15.—Kraus: Ueber die Zuckerumsetzung im menschl. Blute ausserhalb des Gefäss-systems. Z. M. **21.** 315. 1892.—Umber: Zur Lehre von der Glykolyse. Ibid. **39.** 13. 1900.

—Pavy and Siau: Glycolysis in Drawn Blood. J. P. **27.** 451. 1902.—Bendix u. Bickel: Exper. kritische Beitr. zur Lehre von der Glykolyse. Z. M. **48.** 79. 1903.

131. Schmiedeberg: E. A. **14.** 1881.—Jaquet: Ueber die Bedingungen der Oxydationsvorgänge in den Geweben. E. A. **29.** 386. 1892.—Salkowski: Ueber das Oxydationsferment der Gewebe. C. m. W. **1894.** Nr. 52.—Spitzer: Die zuckerzerstörende Kraft des Blutes und der Gewebe. B. k. W. **1894.** 949 and Ar. P. M. **60.** 303. 1895. F. M. **16.** 451. 1898.

132. Jacobi: Ueber die Oxydationsfermente der Leber. Ar. p. A. **157.** 235. 1899.—Blumenthal: Ueber das glykolytische Ferment. D. m. W. **1903.** 961.

133. Stocklasa: Zur Kenntnis der aus der Zelle isolierten gärungserregenden Enzyme. C. P. 1903. Nr. 17. (Bibliography.)—Stocklasa: Die glykoly. Enzyme im tier. Gewebe. D. m. W. **1904.** 198.—Simacek: Beitr. zu Cohnheims "Kohlehydratverbrennung in den Muskeln, etc." Ibid. P. 477.—Sieber: Einwirk. der Oxydationsenzyme auf Kohlehydrate. Z. p. C. **39.** 484. 1903.—Feinschmidt: Ueber das zuckerzerstörende Ferment in den Organen. Be. P. P. **4.** 511. 1904. (Literature on glycolytic ferments.)—Braunstein: Beitr. zur Frage der Glykolyse. Z. M. **51.** 359. 1904.

134. Cohnheim: Die Kohlenhydratverbrennung in den Muskeln und ihre Beeinflussung durch das Pankreas. Z. p. C. **39.** 336. 1903.

135. Hirsch: Glykolyse. Diss. Strassb. 1903 and Be. P. P. **4.** 535. 1904.

136. Arnheim u. Rosenbaum: Beitr. zur Frage der Zuckerzerstörung. Z. p. C. **40.** 220. 1903.—Sehrt: Zur Frage der hepatogenen Lävulosurie. Z. M. **56.** 509. 1905.

137. Claus u. Embden: Pankreas und Glykolyse. Be. P. P. **6.** Pp. 214, 343. 1905.

138. Hoppe-Seyler: Beitr. zur Kenntnis der Beziehungen der Erkrankung des Pankreas und der Gefässe zum Diab. mell. D. Ar. M. **52.** 171. 1894; Ueber chron. Veränderungen des Pankreas bei Arterioskl. und ihre Beziehungen zum Diab. mell. Ibid. **81.** 119. 1904.

139. Dieckhoff: Beitr. zur path. Anat. des Pankreas. Festschr. f. Th. Thierfelder. Leip. 1894.—Williamson: L. 1894.—Hansemann: Die Beziehungen des Pankreas zum Diab. Z. M. **26.** 191. 1894.—Sauerbeck: l. c. (118).

139a. Opie: On the Relation of Chronic Interst. Pancreatitis to the Islands of Langerhans and to Diab. Mell. J. E. M. V. **398,** 527. 1901.—Ssobolew: Zur Morphol. der inneren Sekretion der Bauchspeicheldrüse. Ar. p. A. **168.** 91. 1902.

140. Herxheimer: Zur Frage des Verhaltens der Langerhans'schen Inseln bei Diab. mell. Festschr. f. Orth. 1903.—Ueber Pankreaszirrhose. Ar. p. A. **183.** 228. 1906.—Karakascheff: Ueber das Verhalt. der Langerhans'schen Inseln. D. Ar. M. **82.** 60. 1904.—Reitmann: Pathol. der menschl. Bauchspeicheldrüse. Z. H. **26.** 1. 1905.—Gutmann: Beitr. z. Histol. des Pankreas. Ar. p. A. **177.** Suppl. 1904.

140a. Moore, Edie, and Abrams: Treatment of Diabetes. B. J. 1906. p. 29.

Suprarenal Diabetes.

141. Blum: Ueber Nebennierendiab. D. Ar. M. **71.** 146. 1901; Weitere Mitteil. zur Lehre von dem Nebennierendiab. Ar. P. M. **90.** 617. 1902.

142. Herter and Richards: Glycosuria following Exp. Inj. of Adrenalin. M. N. **1902.** 1 Feb.—Herter and Wakeman: Ueber Adrenalin-Glykos. und verwandte exper. Glykosurien. Ar. p. A. 169. 479. 1902; On Adrenalin Glycosuria and Certain Relations between the Adrenal Glands and Carbohyd. Metab. A. J. M. S. **1903.** Jan.—Vosbourgh and Richards: On the Sugar Contents, etc., after Admin. of Adrenalin. A. J. P. **9.** Mar. 1903.—Aronsohn: Die Zuckerausscheid. nach Adrenalin-Injekt. und ihre Beeinflussung durch künstlich erzeugtes Fieber. Ar. p. A. **174.** 383. 1903.—Noel-Paton: S. J. **1904.** Dec.

142a. Underhill: Exper. Glycosuria. J. B. C. **1.** Oct. 1905.—Araki: Ueber die Bildung von Milchsäure und Glykose bei O_2-Mangel. Z. p. C. **15.** 335 and 546. 1891; **16.** 453. 1892.

142b. Aronsohn: Lit. (142).—Ellinger u. Seelig: Der Einfl. von Fieber, Infektion und Nierenschädigungen auf die Suprarenin-Glykosurie. Mü. m. W.

1905. No. 11.—Cf. also RICHTER: Mü. m. W. **1905.** 656.—ELLINGER-SEELIG. Ibid., p. 680.

143. ZÜLZER: Zur Frage des Nebennierendiab. B. k. W. **1901.** Nr. 48.—METZGER: Zur Lehre vom Nebennierendiab. Mü. m. W. **1902.** Nr. 12.

ACROMEGALY DIABETES.

144. LOEB: Ein Erklärungsversuch der verschied. Temperaturverhält. bei der tuberkulösen Basilarmeningitis. D. Ar. M. **34.** 449. 1884.

145. HANSEMANN: Ueber Akromegalie. B. k. W. **1897.** No. 20.—STRÜMPELL: Akromegalie u. Diabetes. Z. N. **11.**—NAUNYN: l. c. (8). P. 80.—LOEB: Beitr. zur Lehre vom Diab. mell. C. i. M. **1898.** Nr. 35.—WILLIAMSON: Diabetes Mellitus. 1899. P. 137.—SCHLESINGER: Ueber die Beziehungen der Akromegalie zum Diabetes. W. k. R. 1900. Nr. 15.—STERNBERG: Akromegalie in NOTHNAGEL'S Handb. d. sp. Path. u. Ther.—LORAND: Die Entstehung der Zuckerkrank. und ihre Beziehungen zu den Veränderungen der Blutgefässdrüsen. 1903.—L'Origine du Diabète. B. roy. M. **1903.** 2 Mars.—ACHARD ET LOEPER: Gigantisme et Diabète. Gz. h. 1900. Nr. 37.—SALOMON: Ueber den Gaswechsel bei Morb. Based. und bei Akromeg. B. k. W. **1904.** Nr. 24.—STADELMANN: Zur Lehre von der Akromeg. Z. M. **55.** 44. 1904.

ENERGY EXCHANGE.

146. PETTENKOFER U. VOIT: Ueber den Stoffwechselverb. in der Zuckerharnruhr. Z. B. **3.** 380. 1867.—VOIT: Phys. des Stoffwechsels. P. 328. 1881; VOIT: Ueber den Stoffwech. bei Diab. mell. Z. B. **29.** 141. 1892.

147. LIVIERATO: Ueber die Schwankungen der vom Diab. ausgesch. CO_2. E. A. **25.** 161. 1889.

148. EBSTEIN: Beitr. zum respirat. Gaswech. bei der Zuckerkrankh. D. m. W. **1898.** 101.

149. ROBIN ET BINET: Echanges respir. dans le diabète. Ar. g. M. **1898.** 9. 283.

150. EBSTEIN: Ueber die Lebensweise der Zuckerkranken. P. 154. 1898.—EBSTEIN-SCHWALBE: Handb. d. prakt. Med. III. 2 P. 661.—EBSTEIN: Vererbbare zellul. Stoffwechselkrankh. P. 57. 1902.

151. WEINTRAUD U. LAVES: Ueber den resp. Stoffw. im Diab. mell. Z. p. C. **19.** 603. 1894.

152. LEO: Resp. Stoffw. bei Diab. mell. Z. M. **19.** Suppl. P. 101. 1891.—STÜVE: Über den resp. Gasw. bei Schilddrüsenfütterung, bei Morb. Basedowii u. bei Diab. mell. A. K. **1896.** 44.—NEHRING U. SCHMOLL: Einfl. der Kohlenhyd. auf den Gaswech. des Diabetikers. Z. M. **31.** 59. 1897.—MAGNUS-LEVY: Respirationsvers. an diabet. Menschen. Z. M. **56.** 83. 1905.

153. KAUFMANN: La nutrition et la thermogenèse comp. pendant le jeune chez les animaux norm. et diab. C. r. S. B. **1896.** 7 Mars.

154. WEINTRAUD U. LAVES: Ueber den resp. Gasw. eines diab. Hundes. Z. p. C. **19.** 629. 1894.

155. WEINTRAUD: l. c. (102c). P. 18.

156. KOLISCH: Lehrb. d. diätet. Therapie. II. Bd. P. 230. 1900.—Zur Theorie der Diabetesdiät. W. m. W. **1902.** Nr. 20-22.—SCHLESINGER: Ueber das Nahrungsbedürfnis der Diabetiker. Z. d. p. T. **6.** 259. 1903.

157. v. NOORDEN: Lehrb. der Path. des Stoffwechsels. S. 387. 1893.—Die Zuckerkrank. und ihre Behandlung. P. 92. 1901.—LUSK: Ueber den Einfl. der Kohlenhyd. auf den Eiweisszerfall. Z. B. **27.** 459. 1890.—VOIT: l. c. (146).—NAUNYN: l. c. (8).—HIRSCHFELD: Die Zuckerkrankheit. 1902. Pp. 80, 188.—MAGNUS-LEVY: (152).

158. Naturforscherversammlung in Karlsbad. **1902.** Abt. f. inn. Med. 3. Sitzung.

PROTEIN METABOLISM.

159. NAUNYN: Die diät. Behandlung des Diab. mell. Vo. S. V. Nr. 349-350. 1889.—v. NOORDEN: Diab. mell., in v. LEYDEN'S Handb. der Ernährungsth. **2.** 211. 1904.—LENNÉ: Wesen, Ursache und Behandlung der Zuckerkrankheit. 1898.—KOLISCH: Zur Theorie der Diabetesdiät. W. m. W. **1902.** Nr. 20-22.

160. v. VOIT: Physiol. des Stoffwech. P. 226. 1881.

161. Lusk: Ueber den Einfluss der Kohlenhyd. auf den Eiweisszerfall. Z. B. **27.** 459. 1891.

162. Miura: Alkohol als Eiweiss-sparer, in v. Noorden's Beitr. zur Lehre vom Stoffwech. **1.** 1. 1892.—Kayser: Ueber die Bezieh. von Fett und Kohlenhydraten zum Eiweissumsatz. Ibid. **2.** 1. 1894.

163. Hirschfeld: Unterernähr. u. Ueberernährung. 1897.

164. Gähtgens: Ueber den Stoffw. eines Diabetikers, verglichen mit dem eines Gesunden. Diss. Dorpat, 1866.—Voit: l. c. (146).—Weintraud: (102c).—Pautz: Zur Kenntnis des Stoffw. Zuckerruhrkranker. Z. B. **32.** 197. 1895.—Borchardt u. Finkelstein: Zur Lehre vom Stoffw. der Zuckerkranken. D. m. W. **1893.** Nr. 41.—Lauritzen: Kliniske Unders. over Diab. mell. 1897.—Lüthje: l. c. (95).—Ajello u. Cacace: Ueber den Stoffw. bei traumat. Diab. W. m. W. **1904.** 1754.

165. v. Mering: Ueber exper. Diab. V. C. M. **1886.** 185.—v. Noorden: Pathol. des Stoffwech. P. 389. 1893.—Weintraud: l. c. (102c).—Lüthje: l. c. (95).

166. Magnus-Levy: Die Oxybuttersäure. E. A. **42.** 149. — Lüthje: Kasuistik zur Klinik u. Stoffwech. des Diab. mell. Z. M. **43.** 225. 1901.

167. Münzer u. Strasser: Ueber die Bedeut. der Azetessigsäure für den Diab. mell. E. A. **32.** 372. 1893.

168. Wegeli: Beitr. zur Kenntnis des Diab. mell. im Kindesalter. Ar. K. **19.** 1. 1896.—Hesse: l. c. (102a).

168a. Dengler u. Mayer: Ueber Gaswechselvers. bei der N-Mast des Menschen. Ct. P. S. **1.** 8 Ht. 1906.

The Several Carbohydartes of Diabetic Urine.

169. Külz: Ueber das Vorkommen einer linksdrehenden wahren Zuckerart im Harn. Z. B. **27.** 228. 1890.—Seegen: Lävulose im diab. Harn. C. m. W. **1884.** Nr. 43.

170. Czapek: Eine seltene Form des Diab. mell. P. W. **1876.** 265.—Zimmer: Lävulose im Harn eines Diabetikers. D. m. W. **1876.** 329.—May: Lävulosurie. D. Ar. M. **57.** 279. 1896.

171. Rosin u. Laband: Ueber spontane Lävulosurie und Lävulosämie. Z. M. **47.** 182. 1902.—Rosin: Ueber Fruchtzucker-Diab. Salkowski-Festschr. P. 105. 1904.

172. Lion: Ueber gleichzeitiges Auftreten von Fruchtzucker und Traubenzucker im Harn. Mü. m. W. **1903.** 1105.—Schwarz: Untersuch. über Diabetes. D. Ar. M. **76.** 279. 1903.—Umber: Ueber Ausscheid. u. Assim. von Fruchtzucker. Salkowski-Festschr. P. 375. 1904.—Graul: Lävulosurie im Diabetes mellitus. C. i. M. **1905.** No. 7.

173. Pickardt: Zur Chemie pathol. Ergüsse. B. k. W. **1897.** No. 39. Strauss: Die chron. Nierenentzündungen in ihrer Einwirkung auf das Blut. **1902.** —Neuberg u. Strauss: Fruchtzucker in den menschl. Körpersäften. Z. p. C. **36.** 227. 1902.

174. Schlesinger: Zur Klinik und Pathogen. des Lävulosediab. E. A. **50.** 273. 1903.—Bruyn u. Ekenstein: Trav. chim. des Pays-Bas. **14.** Pp. 156, 203.

175. Külz: l. c. (63). **1.** 98.

176. Bohland: Ueber den Einfl. der Lävulose auf die Traubenzuckerausscheid. bei Diab. mell. T. M. 1894. 377.—Haycraft: Lävulose bei Diabetikern. Z. p. C. **19.** 137. 1894.—Stewart: Diabetes treated by Levulose. In. C. IV. Ser. **3.** 78. 1894.—Solis-Cohen: Ibid., p. 66.—Burnotte: Ueber das Verh. der Lävulose im diabet. Organismus. Diss. Freiburg. 1893.—Palma: Ueber die Verwertung der Lävulose und Maltose bei Diab. mell. Z. H. 15. 264. 1894.—v. Mering: in Pentzold-Stintzing's Handb. der spez. Ther. Bd. 2. 1897.—de Renzi u. Reale: Ueber die Zersetzungsfähigkeit der Lävulose. W. m. W. 1897. Nr. 9.—Hale White u. Grube: Ueber die Anwendung der Lävulose bei Diab. mell. Z. k. M. **26.** 332. 1894.—Lindemann u. May: Zur diätet. Behandlung des Diabetes. An. S. K. **1893.** 180. 1895.—Naunyn: l. c. (8). P. 134.—Külz: Klin. Erfahrungen über Diab. mell. (Rumpf). Jena, 1899.—v. Noorden: Lehrb. der Path. des Stoffwech. P. 395. 1893.—Die Zuckerkrankh. und ihre Behandlung. P. 82. 1901.—The Pathol. Chem. of Diab. Mell. and its Treatment. Pp. 34, 48. New York, 1905.

177. v. Noorden: In v. Leyden's Handb. d. Ernährungsther. II. 456. 1898.—Naunyn: l. c. (8). P. 135.—Socin: Lävulose und Milchzucker bei Diabetikern. Diss. Strassb., 1894.—Bohland, Palma: (176).

178. Teschemacher: Zur Behandl. des Diab. mell. Mü. m. W. **1897.** 251. —v. Oefele: Was ist zielbewusste Diabetestherapie. D. Z. **1902.** Nr. 22, 23. **1903.** Nr. 3, 11, 14, 17.

179. le Nobel: Ein Fall von Fettstuhlgang mit gleichzeitiger Glykosurie. D. Ar. M. **43.** 285. 1888.—v. Ackeren: Ueber Zuckerausscheid. durch den Harn bei Pankreaserkrankungen. B. k. W. **1889.** 293.

180. Lépine et Boulud: Maltosurie chez certains diabètiques. C. r. A. S. **132.** 610. 1901.—Kottmann: De la Maltosurie. Thèse de Genève. 1901. (Ma., **1901.** 849.)

181. Baisch: Ueber die Natur der Kohlenhydr. des norm. Harns. Z. p. C. **20.** 249. 1895.—Lemaire: Ueber das Vorkommen von Milchzucker im Harn der Wöchnerinnen. Z. p. C. **21.** 450. 1896.—Pavy and Siau: On the Nature of the Sugar present in Normal Blood, Urine, and Muscle. J. P. **26.** 282. 1901.

182. Worm-Müller: Ausscheid. des Zuckers im Harn nach Genuss von Kohlenhydraten bei Diab. Ar. P. M. **36.** 172. 1885.—de Jong: Over omzetting van Melkzuiker bij diab. mell. Diss. Amsterd. 1886.—Külz: l. c. (63). I. 157.—Bourquelot et Troisier: C. r. S. B. **41.** 142. 1889.—Voit: Ueber das Verhalt. des Milchzuckers beim Diab. Z. B. **28.** 353. 1892.—Naunyn: (8). P. 134.

183. Winternitz u. Strasser: Strenge Milchkuren bei Diabetes. C. i. M. 1899. Nr. 45.

184. Voit: Ueber das Verhalt. der Galaktose beim Diabetiker. Z. B. **29.** 147. 1892.

184a. Grosz: Über Glykosurie im Säuglingsalter. Ja. K. **34.** 83. 1892.—Langstein u. Steinitz: Laktase und Zuckeraussch. bei magendarmkranken Säuglingen. Be. P. P. **7.** 575. 1906.

185. Külz u. Vogel: Ueber das Vorkommen von Pentosen im Harn bei Diab. mell. Z. B. **32.** 185. 1895.

186. v. Alfthan: Ueber dextrinartige Substanzen im diabet. Harn. 1904.

187. Salkowski u. Neuberg: Die Verwandlung von d-Glukuronsäure in l-Xylose. Z. p. C. **36.** 261. 1902.

187a. Ruff: C. B. **31.** 1573. 1898. u. Ueber d- und s-Arabinose. Ibid. **32.** 550. 1899.

188. Cremer: Ueber das Verhalt. einiger Zuckerarten im tier. Organismus. Z. B. **29.** 484. 1892.—Ueber die Verwertung der Rhamnose. Ibid. **42.** 428. 1901.—Frentzel: Ueber Glykogenbild. im Tierkörper Ar. P. M. **56.** 273. 1894.

189. Lindemann u. May: Verwertung von Rhamnose. D. Ar. M. **56.** 282. 1896.

190. v. Jaksch: Ueber aliment. Pentosurie. Z. H. **20.** 195. 1899.

191. Salkowski: Ueber die Gärung der Pentose. Z. p. C. **30.** 478. 1900.

192. Voit: Ueber das Verhalten verschied. Zuckerarten im menschl. Organ. D. Ar. M. **58.** 524. 1897.

193. v. Jaksch: Ueber die aliment. Pentosurie der Diabetiker. D. Ar. M. **63.** 612. 1899.

194. Bergell: Verhalt. der L. Arabinose im norm. u. diabet. Organis.—v. Leyden-Festschr. **2.** 1902.

195. Alfthan: Ueber Benzoylesther und Kohlenhydrat. Diss. Helsingfors, 1900.

196. Thierfelder: Ueber die Bild. von Glykuronsäure beim Hungeriter. Z. p. C. **10.** 163. 1886.—Loewi: Ueber den Einfl. des Kamphers auf die Zuckeraussch. im Phloridzindiab. E. A. **47.** 56. 19.

197. Fischer u. Piloty: C. B. **24.** 522. 1891; **26.** 2403. 1893.

198. Embden: Ueber die Bildung gepaarter Glykuronsäure in der Leber. Be. P. P. **2.** 591. 1902.

199. Neuberg: Die Phys. der Pentosen u. der Glykuronsäure. Er. Ph. **3.** I. Abt. 447. 1904.

200. Mayer u. Neuberg: Ueber den Nachweis gepaarter Glykuronsäuren u. ihr Vorkommen im norm. Harn. Z. p. C. **29.** 256. 1900.—Mayer: Ueber unvollkommene Zuckeroxyd. im Organismus. D. m. W. 1901. Nr. 16 and 17. —Experim. Unters. über Kohlenhydratsäuren. Z. M. **47.** 68. 1902. — Ueber

intermed. Kohlenhydratstoffwech. Ges. f. inn. Med. Wien. 24 März, 1904. —Mayer: Ueber Indoxyl-, Phenol- u. Glykuronsäureaussch. beim Phloridzindiab. Be. P. P. **2.** 217. 1902.

201. Ruschhaupt: Ueber Azetonglykosurie. E. A. **44** 127. 1900.—Müller: Ueber Azetonglykosurie. Ibid. **46.** 61. 1901.—Neubauer: Ueber Glykuronsäurepaarung bei Stoffen der Fettreihe. Ibid. **46.** 133. 1901.

202. Baumgarten: Beitr. zur Kenntnis des Diab. mell. Z. e. P. **2.** 53. 1905.

203. Wohlgemuth: Ueber Glykuronsäurebild. beim Menschen. B. k. W. **1904.** 1084.

204. Bial: Ueber die Ausscheid. der Glykuronsäure. Z. k. M. **47.** 489. 1902.—Esdall: Concerning the Benzoyl Esters of the Urine. U. Pa. **15.** 34. 1902.—Neubauer: l. c. (201).

Glucose in the Urine.

205. Traube: Ueber die Grenze der Zuckerausscheidung. Ar. p. A. **4.** 109. 1852.

206. v. Noorden: Die Zuckerkrankh. und ihre Behandlung. 1901.

207. Seegen and Others: Ueber die Behandl. des Diab. mell. X. I. M. C. **2.** Abt. V. 93. 1890.

208. Leo: Ueber die eiweiss-sparende Wirkung der Kohlenhydrate bei Diab. mell. XI. V. C. M. 195. 1892.—Külz: l. c. (63). **1.** 119 and **2.** 149.—Troje: Ueber Diab. mell. E. A. **26.** 308. 1890.

209. v. Noorden: l. c. (204). P. 75.

210. Rumpf: Ueber die Assimilationsgrösse und den Eiweissumsatz beim Diab. mell. B. k. W. **1898.** 945.—Külz-Rumpf: Diab. mell. Jena, 1899.

210a. Cantani: Der Diab. mell. P. 379. 1880.—Weintraud: Ueber die Aussch. von Azeton, etc. E. A. **34.** 169. 1894.—Naunyn: l. c. (8). P. 154.

211. Mossé: La cure de pommes de terre. Re. m. **22.** 107, etc. 1902.

212. v. Noorden: Bemerk. zur Path. u. Ther. des. Diab. mell. D. Z. **1902.** Ht. 22.—Ueber Haferkuren bei schwerem Diab. mell. **1903.** 817.

213. Preti: Ueber das Verhalt. der Blutserumdiastasen bei Haferkuren. C. S. 1905. No. 7.

214. Sigel: Therap. Beobachtungen. B. k. W. **1904.** Nr. 1.—Langstein: Beitr. zur Kenntnis des Diab. mell. im Kindesalter. D. m. W. **1905.** Nr. 12.—Lüthje: Ueber einige neuere Gesichtspunkte in der Ther. des Diabetes. M. K. **1905.** Nr. 35.

215. Lipetz: Ueber die v. Noordensche Haferkur. Z. M. **56.** 188. 1905.

216. v. Noorden: Pathol. Chem. of Diab. Mell. and its Treatment. 1905. P. 191.

216a. Schade: Ueber die katalytische Beeinflussung der Zuckerverbrennung. Mü. m. W. **1905.** Nr. 36.

217. Arnheim: Das Verh. rektal eingeführter Zuckermengen beim Diabetiker. Z. d. p. T. **8.** 75. 1904. — Orlowski: Ueber die Ausnutzung von Zuckerklystieren bei Diabetikern. Ibid. P. 481.—Bingel: Ausnützung der Zuckerklystiere im Körper des Diabetikers. T. G. **1905.** Okt.—Lüthje: Lit. (214).

218. Külz: Kann in schweren Formen des Diab. die Zuckerausfuhr durch Albuminate gesteigert werden? E. A. **6.** 140. 1876.

219. Naunyn: Die diätet. Behandl. des Diab. mell. Vo. S. V. 349, 350. 1889.—Lenné: Wesen, Ursache u. Behandl. der Zuckerkrankh. 1898.—Kolisch: Zur Theorie der Diabetesdiät. W. m. W. 1902.—Kolisch u. Schumann-Leclerq: Zur Frage der Kohlenhydrat-Toleranz der Diabetiker. W. k. W. **1903.** 1321.

220. Külz: l. c. (63). **2.** 167.

221. Hirschfeld: Die Anwendung des Alkohols bei der Zuckerharnruhr. B. k. W. **1895.** 95.

222. Strümpell: Zur Aetiol. der Glykosurie u. des Diab. B. k. W. 1896. Nr. 46.—Strauss: Zur Lehre von der neurogenen und thyreogenen Glykosurie. D. m. W. 1897. Nr. 18-20.—Reuter: Beitr. zur Frage der Alkoholglykosurie. Ja. H. VII. 77. 1900.—Strauss: 47.

223. Langstein: 74 deutsche Nat.-Versam. Karlsbad, 1902. (Sekt. Med.).

224. Külz: l. c. (63). **1.** 179.—Bourchardat: Ann. pour Thérap. **1865.** 291 (cit. by Külz).—Zimmer: Die Muskeln eine Quelle, die Muskelarbeit ein Heilmittel der Diabetes. 1880.—v. Mering: Zur Path. und Ther. des Diab. V^th^ K. i. M.

171. 1886.—Finkler: Behandl. des Diab. durch Massage. Ibid. 5. 190.—Albu: Einfluss starker Muskeltätigkeit auf den Diab. B. k. W. 1899. Nr. 11.

225. v. Noorden: l. c. (206). P. 78. 1898, and Lit. Nr. 216. P. 45.

225a. Heinsheimer: Ueber die Ursache der Zuckeraussch. im Pankreasdiab. des Hundes. Z. e. P. **2.** 670. 1906.

226. Schupfer: Infl. de quelques états morb. sur le cours du diabète. Ar. i. B. **29.** 439. 1898.—Hirschfeld: Zur Prognose der Glykosurie und des Diab. B. k. W. **1900.** 550.

227. Bussenius: Fibrin. Pneumonie als Komplikation des Diab. mell. B. k. W. **1896.** 293.—v. Noorden: l. c. (206). P. 81. 1898.—Hirschfeld: (226).—Naunyn: (8). P. 142.—Mohr: Ueber den Einfl. fieberhafter Erkrankungen auf die Glykos. beim Diab. Z. M. **42.** 402. 1901 (Literature given).

228. Poll: Ueber aliment. Glykos. bei fieberhaften Infektionskrankh. A. K. Festschr. 1896. P. 59. (See also F. M. **1896.** 501).—Campagnolle: Versuchsreihe über aliment. Glykos. im Fieber. D. Ar. M. **60.** 188. 1898.

229. Manassein: Ueber die Extrakte der Muskeln und der Leber von fiebernden und hungernden Tieren. Ar. p. A. **56.** 220. 1872.—May: Der Stoffwech. im Fieber. Z. B. **30.** 1. 1893.—Rolly: Ueber Wärmestichhyperthermie, etc. D. Ar. M. **78.** 250. 1903.—Hergenhahn: Ueber Glykogen in Leber und Muskulatur nach Unterbindung des Duct. thorac., sowie unter dem Einfl. des Fiebers. A. K. Festschr. 1896. P. 79.

230. Noel Paton: Influence of Fever on Hepatic Glycogenesis. E. H. R. **1894.** 72, and J. P. **22.** 121. 1897.—Richter: Ueber Temperatursteigerung u. aliment. Glykosurie. F. M. **1898.** 321.

231. Kaufmann u. Charrin: Hypoglycémie pyocyanique. C. r. S. B. **1893.** 1 Juill.

232. Colla: Sul glicogene epatico e muscolare in alcune infez. sperim. Ar. i. B. **26.** H. 2. 1896.

233. Nebelthau: Zur Lehre vom Fieber und Diabetes mellitus. Experim. Arch. **46.** 385. 1901.

234. v. Noorden, quoted by Mohr: l. c. (227).—Hirschfeld: (226).—Pavy: On the Acetone Series of Products in Conn. with Diab. Coma. L. **1902.** II. 64, 143, 207, 347.

234a. Lüthje: Einfl. der Aussentemper. auf die Zuckerausscheidung. XXII. V. C. M. 1906. P. 268.

Acetone Bodies.

235. Magnus-Levy: l. c. (166).—Waldvogel: Die Azetonkörper. 1903. Mohr: Ueber diabet. und nicht-diabet. Autointoxik. N. k. A. H. 4. 1904.—Schwarz: Untersuch. über Diab. D. Ar. M. **76.** 233. 1903.—Satta: Ueber die Bedingungen der Azetonbild. im Tierkörper. Be. P. P. **6.** 1. 1904, and 376. 1905.

236. Embden, Salomon, Schmidt: Ueber Azetonbild. in der Leber (Quellen des Azetons). Be. P. P. **8.** Ht. 3, 4. 1906.—Embden u. Kalberlah: Ueber die Azetonbild. in der Leber. Ibid.

236a. Neubauer u. Falta: Ueber das Schicksal einiger aromat. Säuren bei der Alkaptonurie. Z. p. C. **42.** 96. 1904.

237. Flückiger: Ueber die Ca O-reduzierenden Substan. im Harn. Z. p. C. **9.** 323. 1885.—Baer: Ueber die Einwirk. der Glykuronsäureaussch. auf die Azidose. Z. M. **56.** 198. 1905.

238. Hirschfeld: Über Azetonurie u. das Coma diab. Z. M. **31.** 212. 1896, and **28.** 176. 1895.

239. Rosenfeld: Die Grundgesetze der Azeton. und ihre Behandlung. C. i. M. **1895.** Nr. 51.

240. Geelmuyden: Ueber Azeton als Stoffwechselprod. Z. p. C. **23.** 431. 1897; Über Azetonkörper. Sk. Ar. P. **11.** 97. 1900.—Magnus-Levy: l. c. (166). Über Azidosis im Diab. mell. E. A. **45.** 389. 1901.

241. Nasse: Ueber sekundäre Oxydationen. Ar. P. M. **41.** 384. 1887.

242. Geelmuyden: l. c. (240). P. 114. (1900.)—Schwarz: Ueber die Oxyd. des Azetons und homologer Ketone. E. A. **40.** 168. 1897.—Waldvogel: l. c. (235). P. 90.

243. Müller: Ueber Azetonbild. im menschl. Organ. XVI. V. C. M. **1898.** 447.—Schwarz: Geelmuyden: l. c. (242).

244. Geelmuyden: Ueber den Azetongeh. der Organe, etc. Z. p. C. **41.** 128. 1904.

245. Talma: Zur Ernährung der Diabetiker. T. G. **1901.** 385.—Hirschfeld: Über die Azeton. und das Coma diab. Z. M. **28.** 176. 1895.—Waldvogel: Zur Lehre von der Azetonurie. Z. M. **38.** 506. 1899.—Rosenfeld: Lit. Nr. 239.

245a. Borchardt: Ueber den Einfl. des Eiweiss-stoffw. auf die Azetonkörperaussch. E. A. **53.** 388. 1905.

246. Müller: Ueber die Ausscheidungsstätte des Azetons. E. Ar. **40.** 351. 1898.—Schwarz: Ueber Azetonaussch. XVIII. V. C. M. P. 480. 1; also l. c. (235). P. 241.

247. Schwarz: l. c. (235). P. 247.

248. Külz: Ueber eine neue linksdrehende Säure. Z. B. **20.** 165. 1884.

249. Weintraud: l. c. (251).—Schwarz: (235). P. 247.—Magnus-Levy: (240).—Geelmuyden: (244). P. 150.

250. Magnus-Levy, Schwarz: l. c. (235).—Mohr u. Loeb: Beitr. zur Frage der diabet. Azidosis. C. S. **3.** 193. 1902.

251. Weintraud: Ueber die Ausscheid. von Azeton, Diazetsäure, Oxybuttersäure bei Diab. mell. E. A. **34.** 169. 1894. Hart: A. J. M. S. 1906. P. 220.

252. Schwarz: l. c. (235).—Loeb u. Mohr: (250).

253. v. Noorden: l. c. (212). 1902.

254. Waldvogel, Satta: l. c. (235).—Schwarz: (235 and 246).—Lépine: Traitement du diab. sucré. Se. M. **1901.** 361.—Zaudy: Beitr. zur Lehre von der Lipämie. D. Ar. M. **70.** 301. 1900.—Hesse: Ueber Eiweissumsatz und Zuckeraussch. des schweren Diabetikers. Z. M. **45.** 237. 1901.—Joslin: Influence of Various Fats on the Formation and Excretion of Acetone. J. M. R. **12.** 433. 1904.—Grube: Z. d. p. T. **6.** 75. 1903.

255. Satta: l. c. (235). 1905.—Mohr: (235).

255a. Meyer: Beitr. zur Lehre von der Azetonurie. Diss. Strassb. 1895.—Satta: Lit. Nr. 235.

256. v. Noorden: Die Zuckerkrankh. und ihre Behandlung. P. 109. 1901.

256a. v. Jaksch: Aceton. u. Diaceturie. 1885.—Wolpe: l. c. (266).—Weintraud: (102c and 251).—Herter: Acid Intoxication of Diab. J. E. M. **5.** 617. 1901.—Pavy: l. c. (234).

257. Stadelmann: Ueber die Ursachen der pathol. NH_3-Aussch. beim Diab. E. A. **17.** 419. 1883.

258. Minkowski: Ueber das Vorkommen von Oxybuttersäure im Harn. E. A. **18.** 35. 1884.—Külz: l. c. (248).

259. Walter: Wirkung der Säuren auf den tier. Organismus. E. A. **7.** 148. 1877.

260. Minkowski: Ueber den CO_2-Gehalt des Blutes bei Diab. mell. Mit. K. P. 174. 1888; and l. c. (258).—Kraus: Pathol. der Autointoxikationen. Er. P. II. 571. 1895.—Naunyn: l. c. (8. P. 179).—Magnus-Levy: (166 and 240).

261. Saundby: Renal and Urinary Dis. 1896.—Williamson: Diabetes Mellitus. 1898.—Lépine: Le Diabète et son traitement. 1899.—v. Noorden: l. c. (206).—v. Mering: Diabetes in Pentzold-Stintzing's Handb. der spez. Ter. Bd. 2. 1897.

262. Rumpf: Ueber Diab. mell. B. k. W. **1895.** Nr. 31 and 32.

263. Grube: Ueber ein dem Coma diab. analoges, künstlich hervorgerufenes Coma. XVIII. V. C. M. 199. **1900.**—Sternberg: Chem. u. Experim. zur Lehre vom Coma. Z. M. **38.** 65. 1899.

264. Magnus-Levy: l. c. (240). P. 426.

265. Hugounenq: De la prés. de l'acide β-oxybut. dans le sang diab. C. r. S. B. 19. III. 1887.—Minkowski: Ueber den CO_2-Gehalt des Blutes beim Diab. u. im Coma diab. Mit. K. **1888.** 174.—Magnus-Levy: l. c. (166).

265a. Schittenhelm u. Katzenstein: Ueber die Beziehungen des Ammoniaks zum Gesamtsticks. im Urin. Z. e. P. **2.** 542. 1906. (Full bibliography.)

266. Wolpe: Über die Oxybuttersäure des diab. Harns. E. A. **21.** 159. 1886.—Stadelmann: l. c. (257).—Magnus-Levy: (240).

267. Wolpe: l. c. (266).—Weintraud: (251).—Magnus-Levy: (240).—Gerhardt u. Schlesinger: Ueber Kalk- und Magnesiaaussch. beim Diab. E. A. **42.** 83. 1899.—Külz-Rumpf: Diab. mell. P. 430. Jena, 1899.

267a. Magnus-Levy: Lit. Nr. 240 (1901).

268. Weintraud: l. c. (251).—v. Noorden: (256). P. 110.—Sandmeyer, in Külz: Über Diab. mell. P. 446. Jena, 1899.—Naunyn: l. c. (8). P. 183.

269. Wolpe: l. c. (266).—Minkowski: (265).—Frerichs: Ueber den Diab. P. 119. 1884. (The normal value is higher than Frerichs' standard).—Mya e Tassinasi: Sulle variazione della reaz. alcal. del sang. Ar. S. M. **9.** Nr. 20. 1886.—v. Jaksch: Ueber diab. Lipacidurie und Lipacidämie. Z. M. **11.** 307. 1886.—Lépine: Sur la pathog. et le traite. du coma diab. Re. m. **7.** 224. 1887. —Rumpf: Alkalimet. Untersuch. des Blutes. Diss. Kiel. 1891.—Orlowski: Zur Frage über die Blutalkaleszenz. C. S. **3.** 31. 1902.—Kraus: Ueber die Alkaleszenz des Blutes in Krankh. Ar. H. **10.** 106. P. 889.

270. Böcker: Über Diab. mell. D. K. **5.** 359. 1853.—Neubauer: Ueber die Erdphosphate des Harns. J. p. C. **67.** 64 and 83. 1856.—Toralbo: Sull' eliminazione del calcio per le urine. Ri. c. 1889. Juin, cf. C. i. M. **1890.** P. 19.

271. v. Ackeren: Cf. v. Noorden: Path. des Stoffw. P. 416. 1893.

272. v. Limbeck: Zur Lehre von der Säurevergiftung. Z. M. **34.** 439. 1898.—Tenbaum: Ueber Kalkaussch. durch den Harn bei Diab. Z. B. **33.** 379. —v. Moraczewski: Stoffwechselvers. bei Diab. Z. M. **34.** 59. 1898.

273. Gaehtgens: Ueber den Stoffw. eines Diabetikers. Diss. Dorpat, 1866.

273a. Kraus: Zur Lehre von der Säurevergiftung. P. W. 1899. Nr. 14, and Lit. Nr. 269.

274. Binz: V. C. M. 175. 1886.—Mayer: Ueber die toxische Wirk. der niederen Fettsäuren. E. A. **21.** 119. 1886.

275. Frerichs: Plötzlicher Tod u. Coma diab. Z. M. **6.** 1. 1883.—Albertoni: Azetonämie u. Diab. E. A. **18.** 218. 1884.—v. Jaksch: Azetonurie und Diazeturie. 1885.

276. Araki: Zur Kenntnis der Oxybuttersäure. Z. p. C. **18.** 1. 1894.—Meyer: Exper. Beitr. zur Lehre von der Azetonurie. Diss. Strassb. 1895.—Sternberg: Zur Kenntnis der Wirk. der Buttersäure u. β-Oxybuttersäure. Ar. p. A. **152.** 207. 1898.—Zeehuysen: Über Azidität. Ma. **1899.** P. 825.—Minkowski: l. c. (117). 1893.—Schwarz: Ueber die Oxyd. des Azetons und homologer Ketone der Fettsäurereihe. E. A. **40.** 168. 1898.—Waldvogel: l. c. (235). P. 236.

277. Wilbur: Acidosis. J. A. M. A. 22. X. 1904.

277a. Gamble: Alkalinity of Blood. J. P. & B. 1906. XI. 24.

The Individual Urinary Constituents.

278. Külz: l. c. (63), u. Külz-Rumpf: (210).

279. Quincke: Zur Path. der Harnsekretion. XII. V. C. M. **1893.** 380.

280. Pick: Ueber die Aussch. des Wassers bei Diab. mell. P. W. **1889.** Nr. 29.

281. Gumlich: Ueber die Aussch. des N im Harn. Z. p. C. **17.** 10. 1892.—v. Noorden: Path. des Stoffw. P. 411. 1893.—Richter: Ueber die Verteil. des N im Harn unter path. Verhältnissen. Ch. An. **22.** 287. 1897.—Magnus-Levy: l. c. (240).—v. Jaksch: Über die Verteil. der N-haltigen Substanzen im Harn des kranken Menschen. Z. M. **50.** 167. 1903.

282. Schittenhelm u. Katzenstein: Ueber die Beziehungen des Ammon. zum Gesamt-N. Z. e. P. **2.** 542. 1906.

283. Magnus-Levy: l. c. (240).—Lüthje: Kasuistis. zur Klin. des Diab. mell. Z. M. **43.** 225. 1901.—Camerer: Über die NH_3-Ausscheid. im menschl. Harn. Z. B. **43.** 13. 1902.

284. Külz: Die Harnsäurebestim. bei Diab. mell. D. A. **1872.** 293.—Naunyn u. Riess: Die Harnsäureaussch. Ibid. **1869.** 381.—Startz: Ueber Harnsäureaussch. bei Diab. mell. Diss. Freiburg. 1891.

285. Bischofswerder: Ueber Harnsäure- und Alloxurbasenaussch. bei Diab. mell. Diss. Berl. 1896.—Jacobi: Ueber die Aussch. der N-haltigen Harnbestandteile bei Diab. mell. Z. M. **32.** 557. 1897.—Richter: l. c. (281). Mandel u. Lusk: Stoffwechsel-Beobacht. an einem Fall von Diab. D. Ar. M. **81.** 472. 1904.

286. Lüthje: Lit. Nr. 95 (1900).

287. Laquer: Ueber das Verhalt. der Ausscheid. beim Gebrauche des Hefeextraktes "Wuk." Z. d. p. T. **7.** 332. 1903.

288. Mohr u. Kaufmann: Beitr. zur Alloxurkörperfrage. D. Ar. M. **74.** 359. 1902.

289. v. Noorden: Diab. Mell. P. 115. New York, 1905.
290. Maly: Zur Chem. des diabet. Harns. W. m. W. **1862.** 310.—Gähtgens in Hoppe-Seyler's Med.-chem. Unters. P. 301. 1868.—Hofmann: Ueber Kreatinin im Harn. Ar. p. A. **48.** 358. 1869.—Bouchardat: De la Glycosurie. 1883. P. 20.—Senator: Diabetes. Ziemssen's Handb. d. spez. Path. u. Ther. P. 436. 1878.
291. Bunge: Text-Book of Physiological and Pathological Chemistry. 2nd Engl. Ed. by Starling. 1902.
292. Winogradow: Beitr. zur Lehre vom Diab. mell. Ar. p. A. **27.** 533. 1863.—Stopezansky: Ueber Kreatinins im Harn. W. m. W. **1863.** Nr. 21-25. —Senator: l. c. (290).
293. Folin: Laws governing the Chem. Compos. of Urine. A. J. P. Feb., 1905.
294. Lehmann: Physiol. Chemie. **1.** 203. 1850.
295. Bouchardat: l. c. (290). P. 17.
296. Lewin: Beitr. zum Hippursäurestoffw. des Menschen. Z. M. **42.** 388. 1901.
297. Landau: Ueber die N-Verteilung im Harn. D. Ar. M. **79.** 417. 1904. —Mörner: Zur Bestimm. des Harnstoffs. Sk. Ar. P. **14.** 297. 1903.
298. Satta: Bemerkungen über die N-Verteilung im Harn. Be. P. P. **6.** 358. 1905.
299. Fischer u. Bergell: Ueber die β-Naphtalinsulfoderivate der Aminosäuren. C. B. **1902.** 3779.
300. Plaut u. Reese: Ueber das Verhalt. von in den Tierk. eingeführten Aminosäuren. Ibid. P. 425.—Abderhalden: Abbau und Aufbau der Eiweisskörper. Z. p. C. **44.** 40. 1905.—Bergell u. Blumenthal: Ueber den Einfl. des Pankreas auf den Eiweissabbau. Ar. P. M. **103.** 627. 1904.—Mohr: Ueber die Aussch. von Aminosäuren im diab. Harn. Z. e. P. **2.** 665. 1906.— Embden u. Reese: Ueber die Gewinnung von Aminosäuren aus norm. Harn. Be. P. P. **7.** 411. 1905.
301. Bergell u. Blumenthal: Ueber einen neuen Befund beim Eiweissabbau des Diabetikers. Z. e. P. **2.** 413. 1905.
302. Bouchard: Sur les condit. pathogén. des albumin. qui ne sont pas d'origine rénale. G. m. P. **1892.** P. 475.—Schmitz: Ueber die prognos. Bedeut. und die Aetiol. der Album. bei Diabetes. B. k. W. **1891.** 373.—Grube: Ueber die verschied. Formen der beim Diab. vorkommenden Albuminurien. XVI. V. C. M. **1898.** 95.—v. Noorden: Zuckerkrankheit. P. 102. 1901.—Aldehoff: in Külz's Klin. Erfahrungen über Diab. mell. 449. Jena, 1899.
303. Albertoni: Die Wirkungen und Verwandl. einiger Stoffe im Organismus. E. A. **18.** 236. 1884.—Albertoni u. Pisenti: Wirk. des Azetons und der Azetessigsäure auf die Nieren. Ibid. **23.** 393. 1887.—v. Jaksch: Epilepsia acetonica. Z. M. **10.** 362. 1886.—Dreschfeld: Diabetic Coma. B. M. J. **1886.** Nr. 1338.—Baginsky: Ueber Azeton. bei Kindern. Ar. K. **9.** 1. 1888. —Schwarz: l. c. (235). — Ruschhaupt: Ueber Azetonglykosurie. E. A. **44.** 127. 1900.
304. Schupfer: L'albumin. nel diab. ed il diab. renale. P. **7.** 1900.
305. Ebstein: Ueber Drüsenepithelnekrosen bei Diab. mell. D. Ar. M. **28.** 143. 1881.
306. Külz: Zur Kenntnis der Komazylinder. Diss. Marburg, 1885.—Aldehoff: in Külz's Klin. Erfahrungen über Diab. Jena, 1899. P. 449.—Sandmeyer: Ueber einige Untersuch. mit Demonstrationen. X. V. C. M. **1891.** 341.
307. Rumpf: l. c. (210).—Lenhartz: Mikros. und Chem. am Krankenbett. P. 301. 1901.—Domansky u. Reimann: Ueber die Külzschen Zylinder. Z. H. **22.** II. 226. 1901.—Waldvogel: Die Azetonkörper. P. 259. 1903.
308. Naunyn: l. c. (8). P. 293.
309. Leo: Ueber den Fermentgeh. des Urins. VII. V. C. M. P. 369. **1888.** —Bendersky: Ueber die Aussch. der Verdauungsfermente. Ar. p. A. **121.** 554. 1890.—Stadelmann: Ueber den Pepsinfermentgeh. des Harns. Z. B. **25.** 208. 1889.—Grützner: Ueber Fermente im Harn. D. m. W. **1891.** Nr. 1.
310. Bouchardat: l. c. (290). P. 38.—Minkowski: Ueber den CO_2-Geh. des Blutes bei Diab. mell. Mit. K. **1888.** 174.
311. Rumpf: Diab. mell. B. k. W. **1895.** 669, 700.
312. Strauss u. Philippsohn: Ueber die Aussch. enterogener Zersetzungsprod. Z. M. **40.** 369. 1900.

313. Magnus-Levy: Ueber die Säurebild. bei der Autolyse der Leber. Be. P. P. **2.** 261. 1902.

314. Cantani: Path. u. Ther. der Stoffwechselkrankh. **2.** 1880.

315. Czapek: Beitr. zur Kenntnis der Oxalsäure beim Menschen. Z. H. **2.** 348. 1881.

316. Fürbringer: Zur Lehre vom Diab. mell. D. Ar. M. **16.** 499. 1875.

317. Kisch: Oxalsäureaussch. bei Diab. mell. D. m. W. **1893.** Nr. 28.

318. Mohr u. Salomon: Zur Physiol. u. Pathol. der Oxalsäurebild. u. Ausscheid. D. Ar. M. **70.** 501, 510. 1901.

319. Luzzatto: Ueber die Beziehungen zwischen Oxalsäureaussch. und Glykosurie. Salkowski-Festschr. P. 239. 1904.

320. Moraczewski: Ueber die Ausscheid. von Oxalsäure, Indikan und Azeton bei Diab. Z. M. **51.** 475. 1903.

321. Frerichs: Diab. mell. P. 41. 1884.—Senator: Ueber Indikan-und Kalkaussch. in Krankheiten. C. m. W. **1877.** Nr. 20.—Naunyn: l. c. (8). P. 175.—Fürbringer: l. c. (316).

322. Mayer: Exper. Untersuch. über Kohlenhydratsäuren. Z. M. **47.** 104. 1902.

323. Guiard, Duménil, L. Thomas, cited by Senator: Ueber Pneumaturie. Virchow-Festschr. **3.** 319. 1891.

324. Müller: Ueber Pneumaturie. B. k. W. **1889.** Nr. 41.

325. Schmitz: Cystitis als Komplikation von Diab. B. k. W. **1890.** 515.

326. Külz: l. c. (63). I. 31. (Bibliography.)

327. Reale u. Velardi: Sul' eliminazione dello solfor neutro per le urine. Ar. V. **2.** 141. 1896.

328. Harnack u. Kleine: Ueber den Wert genauer S-Bestimmungen. Z. B. **37.** 417. 1899.

329. Gährgens: l. c. (164).—Külz: (48).—Moraczewski: (42).

330. Rumpf: Ueber die Assimilationsgrösse und den Eiweissumsatz beim Diab. mell. B. k. W. **1898.** 945.

331. Külz: l. c. (63).—Moraczewski: (42).—Tenbaum: (272).

The Blood.

332. Leichtenstern: Ueber den Hämoglobingeh. des Blutes. P. 58. 1878.—Reinert: Die Zählung der Blutkörperchen. P. 200. 1891.—Hayem: Du Sang. 1889.—Grawitz: Klin. Path. des Blutes. P. 425. 1902.—Peiper: Spezifis. Gewicht des menschl. Blutes. C. i. M. **1981.** 223.—Hammerschlag: Spezifis. Gewicht des Blutes in Krankh. Ibid. P. 825.—Copeman: The Spec. Gravity of the Blood. B. M. J. 1891. 1. 161.—v. Jaksch: Ueber die Alkaleszenz des Blutes in Krankh. Z. M. **13.** 350. 1888.—Ueber den N-Gehalt der roten Blutzellen. Ibid. **24.** 429. 1894.—Stintzing u. Gumprecht: Wassergeh. und Trockengeh. des Blutes. D. Ar. M. **53.** 265. 1894.

333. Jakuschewsky: Ueber die klin. Bedeut. der Beständigkeit der roten Blutkörperchen bei verschied. Krankh. R. m. R. **1904.** Nr. 6.

334. Meyer: Die klin. Bedeut. der Eosinophilie. 1905. P. 53.

335. Lécorché: Diabète. P. 238. 1877.

336. Rumpf: Zur Entstehung des Coma diab. S. n. G. 20 Jan., 1902.—Diab. mell. Z. M. **45.** 260. 1902. — Dennstedt u. Rumpf: Über die chem. Zusammensetz. des Blutes u. verschied. menschl. Organe. Mit. H. **3.** 1. 1900.

337. Magnus-Levy: l. c. (240).

338. Grawitz: Klin.-exper. Blutuntersuch. Z. M. **22.** 411. 1893.

339. Landau: Über den osmotisc. Druck des Blutes. D. Ar. M. **78.** 479. 1903.

340. Dennstedt u. Rumpf: Über die chem. Zusammensetz. des Blutes, etc. Z. M. **58.** 84. 1905, and l. c. (336).—Erben: Ueber die chem. Zusammensetz. des Blutes. Z. H. **1995.** 1.

341. Winterberg: Ueber den NH_3-Geh. des Blutes. Z. M. **35.** 417. 1898.

342. Jolles u. Winkler: Ueber die Beziehungen des Harneisens zum Bluteisen. E. A. **44.** 464. 1900.—Jolles: Zur Bestim. des Eisens im Blute.—W. m. P. **1898.** Nr. 5.

343. Mitulescu: Hämatologie. C. i. M. **1904.** Nr. 6.

344. Gumprecht u. Stintzing: l. c. (1).

345. Rosin u. Jellinek: Färbekraft und Eisengeh. des menschl. Blutes. Z. M. **39.** 109. 1900.

346. Damaskin : Zur Bestim. des Eisengeh. des Menschenharns. In Kobert's Arbeiten. **7.** 40. 1891.—Hoffmann : Ueber die Bestim. des Eisens im norm. u. path. Harn. Z. a. C. **40.** 73. 1901.

347. Ehrlich, quoted by Frerichs : Plötzlicher Tod im Coma diab. Z. M. **6.** 31. 1883.—Gabritschewsky : Mikros. Unters. über Glykogenreak. im Blute. E. A. **28.** 272. 1891.

348. Hirschberg : Über die Jodreaktion des Blutes. Z. M. **54.** 223. 1904.

349. Lépine et Barral : Sur les variat. des pouvoirs glycoly. et sacharifiant du sang. 1891. C. r. A. S. 28 Déc., **1891.**—Kaufmann : Sur le pouvoir sacharifiant du sang. C. r. S. B. **1895.** 130.—Achard et Clerc : Variations pathol. du pouvoir amylolytique de sérum sanguin. C. r. S. B. **1901.** 29 Juin.

350. Lépine et Boulud : Sur les leucomaines diabétogènes. C. r. A. S. **1902.** 9 Juin. Sur l'exist. de leucomaines diabétogènes. B. k. W. **1902.** 346.

351. Sweet : Reactions of Blood in Experim. Diab. Mell. J. M. R. **10.** 255. 1903.

351a. Beddard, Pembrey, and Spriggs : Blood Gases in Diabetes. L. 1903. I. 1366.

Lipæmia.

352. Zaudy : Beitr. zur Lehre von der Lipämie und vom Coma diab. D. Ar. M. **70.** 301. 1901.—Fischer : Ueber Lipämie und Cholesterämie. Ar. p. A. **172.** 30. 1903.

353. Bönninger : Ueber die Meth. der Fettbestim. im Blute. Z. M. **42.** 65. 1901.—Rumpf : Ueber den Fettgeh. des Blutes. Ar. p. A. **174.** 163. 1903.

354. Schwarz : Diabetes. D. Ar. M. **76.** 270. 1903.

355. Neisser u. Derlin : Ueber Lipämie. Z. M. **51.** 428. 1904.

356. Ebstein : Zur Lehre von der Lipämie. Ar. p. A. **155.** 571. 1899.

357. Stadelmann : Ueber Lipämie bei Diab. mell. D. m. W. **1902.** Nr. 49. p. 349.

358. Cohnstein u. Michaelis : Ueber die Veränderung der Chylusfette im Blute. Ar. P. M. **65.** 473. 1897 ; **69.** 76. 1898.

359. Pflüger : Die Resorp. der Fette vollzieht sich dadurch, dass sie in wässrige Lösung gebracht werden. Ar. P. M. **86.** 1. 1901.

360. Hanriot : Sur la mécan. des réactions lipolytiques. C. r. S. B. **1901.** 367.

360a. Hale White : Diabetic Lipæmia. L. 1903. P. 1007.

Colour Reactions.

361. Williamson : Eine leichte Methode das Blut eines Diabet. von dem Blute eines Nicht-Diabet. zu unterscheiden. C. i. M. **1897.** Nr. 33.

362. Bremer : An Improved Method of Diagnosticating Diab. from a Drop of Blood. N. Y. J. 7 Mar. **1896.**—Die Diag. des Diab. mell. aus dem Blute mittels Anilinfarben. C. i. M. **1897.** Nr. 22.

363. Goff : Sur certaines réactions chrom. du sang dans le diab. sucré. 1897.

364. Hartwig : Ueber die Farbenreak. des Blutes bei Diab. mell. (Bremersche Reak.). D. Ar. M. **62.** 287. 1899.

365. Lépine et Lyonnet : Sur la réact. de Bremer dans le sang diab. L. m. **1896.** 7 Juin.—Marie et Goff : Sur la réaction de Bremer. Se. m. **1897.** 170.—Patella e Mori : Reazioni chrom. del sangue dei diab. G. O. **1896.** 15 Nov.—Eichner u. Fölkel : Ueber abnorme Blutfärbungen bei Diab. mell. W. k. W. **1897.** Nr. 46.—Loewy : Über das Verhalt. des diabet. Blutes zu den Anilinfarbstoffen. F. M. **1898.** 171.—Strauss : Ueber das Nebeneinander-Vorkommen von Idiotie und Diab. mell. D. Ar. M. **65.** 610. 1900.—Schneider : Zur Bedeut. der Bremerschen Probe. Mü. m. W. **1899.** Nr. 25.

Saliva.

366. Jawein : Zur klin. Path. des Speichels. W. m. P. **1892.** Nr. 15, 16.—Robertson : The Activity of the Saliva in Dis. Conditions. J. P. and B. **7.** 118. 1901.

367. Külz : l. c. (63). II. 134.—Maly in Hermann's Handb. d. Phys. **5.** 2. P. 9. 1881.—v. Jaksch : Clinical Diagnosis. 5th Ed. by Garrod. 1905.—Kühne : Physiol. Chemie. P. 24. 1868.

368. Fleckseder : Beobach. am gemischten Speichel von Gesunden und Kranken. C. i. M. **1905.** 41.

369. Weyert : Uebergang von Blutzucker in verschiedene Körpersäfte. Ar. P. **1891.** 187.

370. Schuman-Leclerq : Ueber den Einfl. der Nahrung auf die Azetonaussch. W. k. W. **1901.** Nr. 10.

371. v. Noorden : Pathol. des Stoffwech. P. 249. 1893.—Nebelthau : Azetonurie. C. i. M. **1897.** 977.

372. Geelmuyden : l. c. (244).—Schwarz : (246).

373. Magnus-Levy : l. c. (240).—Geelmuyden : (244).

374. Lehmann : Physiol. Chemie. **1.** 98. 1850.

375. Limpricht : cit. by Hoppe-Seyler : Lehrb. d. phys. Ch. p. 201. 1880.

376. Sticker : Bedeutung des Mundspeichels. P. 12. 1889.

377. Mosler : Ueber die Beschaffenheit des Parotissekretes bei Diab. mell. Ar. H. **5.** 228. 1864.

378. Sticker : l. c. (11). P. 136.

The Stomach.

379. Honigmann : Ueber Magentätigkeit bei Diab. mell. D. m. W. **1890.** Nr. 43.

380. Fouconnet : Ueber Magen- und Darmtätigkeit bei Diab. mell. Thèse de Genève. 1904.

381. Riegel : Diag. der Magenkrankh. Z. M. **12.** 426. 1887.—Krause : Ueber die Magenfunk. bei Diabetes. Diss. Giessen, 1890.—Honigmann : l. c. (14.).—Gans : Ueber die Magenfunk. bei Diab. mell. V. C. M. **9.** 286. 1890.—Fouconnet : l. c. (15).—Rosenstein : Ueber das Verhalt. des Magens bei Diab. mell. B. k. W. **1890.** 289.

382. v. Noorden : Zuckerkrankheit. P. 113. 1901.

Absorption of Food.

383. Traube : Ueber die Verdauung des Fettes bei Diab. mell. Ar. p. A. **4.** 148. 1851.—Külz : l. c. (63). **1.** 57. (Fæces were only weighed.).—Block : Über die Einwirk. der Kost im Diab. D. Ar. M. **25.** 470. 1880. (Fat resorption.)

384. Voit u. Pettenkofer : l. c. (146).—Hirschfeld : Ueber eine neue klin. Form des Diab. Z. M. **19.** 326. 1891.—Leo : Ueber die eiweiss-sparende Wirk. der Kohlenhydr. bei Diab. mell. V. C. M. **11.** 195. 1892.—v. Noorden : Path. des Stoffw. P. 389. 1893.—Weintraud : Ueber den Stoffw. im Diab. mell. Bib. M. H. 1. 1893. Dapper : Ueber den Einfl. der Kochsalzquellen auf den Stoffw. in v. Noorden's Beitr. z. Path. u. Ther. des Stoffw. H. 5. 1904.—Strauss : Zur Kenntnis der Fettresorp. im Diab. mell. Diss. Strassb. 1893.

385. Heller : Ueber Diab. mell. Heller's Arch. 1852. P. 403.—Rössler : Ueber das Vorkom. von Zucker im Stuhl der Diabetiker. Z. H. **22.** II. 302. 1901.—Orlowski : l. c. (217).

386. Deucher : Stoffwech.-Untersuch. bei Verschluss des Ductus pancreat. K. S. **1898.** 321, 361.—Schild u. Masuyama : Ueber die Behandl. der diabet. Steatorrhoe mit Pankreaspräparaten. Z. d. p. T. **3.** 451. 1900.—Salomon : Ueber Fettstühle. XX. V. C. M. 244. **1902.**—Zur Organother. der Fettstühle. B. k. W. **1902.** Nr. 3.—Weintraud : Die Bedeut. des quantitat. Stoffwechselvers. für die Diagnostik. Die Heilkunde. **1898.** 67.—Wegele : Zur Diag. u. Ther. des Pankreasdiab. F. M. **20.** 313. 1902.

387. Abelmann : Ausnutz. der Nahrung nach Pankreasexstirp. Diss. Dorpat, 1890.

388. v. Noorden : Zuckerkrankheit. 117. 1898.—Schild u. Masuyama : l. c. (21).

Intestinal Putrefaction.

389. Blumenthal : Ueber Glykuronsäure-Ausscheid. Eng. A. **1901.** Suppl. 275.—Ueber Indoxylurie. Ibid. **1902.** 347.—Ueber die Aussch. von Indoxyl als Zeichen einer Stoffwechselstörung. Leyden-Festschr. **2.** 267. 1902.—Blumenthal u. Rosenfeld : Ueber die Entstehung des Indikans im tier. Organismus.

Ch.-An. **27.** 46. 1902.—Lewin: Ueber die Bild. von Phenol und Indoxyl im intermed. Stoffwech. Be. P. P. **1.** 472. 1902.

390. Carletti: Sull' origine delle sostanze aromatiche nell' organismo. A. F. **7.** 323. 1899.—Reale: Sull' indicano e sull' acido glicuronico dell' orina e loro valore clin. N. C. T. **3.** Nr. 5.—Gilbert et Weil: De l'indicanurie physiol. et expérim. chez l'homme sain. C. r. S. B. 7 Juill., 1900.—Moraczewski: l. c. (320).

391. Ellinger: Die Indolbild. und Indikanaussch. beim hungernden Kaninchen. Z. p. C. **39.** 44. 1903.—Mayer: Ueber Indoxyl-, Phenol- und Glykuronsäure-Aussch. beim Phloridzindiab. Be. P. P. **2.** 217. 1902.—Jaffé: Die Indikanurie. D. K. **11.** 219. 1903.

392. Otto: Das Vorkommen grosser Mengen von Indoxyl- und Skatolschwefelsäure im Harn bei Diab. Ar. P. M. **33.** 607. 1884.—v. Noorden: Pathol. des Stoffw. P. 405. 1893.—Strauss u. Philippsohn: Ueber die Aussch. enterogener Zersetzungsprod. im Harn bei konstanter Diät. Z. M. **40.** 369. 1900.—Moraczewski: l. c. (320).

393. Leo: Wesen u. Ursache der Zuckerkrankheit. S. 109. 1900.

394. Strasser: Ueber Phenolaussch. bei Krankheiten. Z. M. **24.** 543. 1894.

395. Neuberg: Ueber die quantitat. Bestim. des Phenols im Harn. Z. p. C. **27.** 123. 1899.

396. Lipetz: Ueber die Wirk. der v. Noorden's Haferkur bei Diab. mell. Z. M. **56.** 188. 1905.

397. Schmitz: Ueber die Behandl. des Coma diab. B. k. W. **1890.** 772.

398. Dominicis: Sur la pathogénie du diab. Ar. m. ex. **1893.** 469.—Töpfer u. Freund: Glykosurie. W. k. W. **1899.** Nr. 51.

399. Lépine: l. c. (21). B. k. W. **1905.**—Leo: l. c. (28). P. 107.

CHAPTER II

GOUT

By CARL von NOORDEN.

Translated by R. W. Webster, M.D., Chicago.

In my treatise on "The Pathology of Metabolism," in which all the known facts regarding the metabolism in gout were, for the first time in many years, collected and critically reviewed, I wrote: "The literature of gout is a very voluminous one. The symptomatology and the variable course of the disease have been frequently discussed in a very thorough manner. The leading scientific investigators have devoted their best efforts to the solving of the questions dealing with the theory of gout, yet our knowledge concerning its metabolic processes stands in marked contrast to the amount of thought expended upon the elaboration of its theory. Only a few details, and, perhaps, even only a few accessory details, of its metabolism have been thus far worked out."

Since then a large number of investigations on gout have been carried out. The researches of Kössel on the cleavage products of nucleinic acid, the recognition of the close relationship between nuclein decomposition and uric-acid excretion [Horbaczewski and others], and the discovery of the chemical constitution of uric acid and its related purin bodies [Fischer], furnished the incentive to more exact observations upon this long-neglected chapter of metabolism. Many new facts became known, yet a clear insight into the dynamics of the metabolic disturbances of gout has not yet been obtained. Thus the two recent extensive and excellent monographs which are devoted to the metabolic pathology of gout [O. Minkowski, H. Wiener (1)] end with the discordant note of *non ignoramus*. The doubt which I expressed twelve years ago, whether uric acid was really the *materia peccans* of gout, and whether the characteristic behaviour of uric acid in gout—that is to say, its accumulation in the blood and its deposition in the tissues—was not a secondary process, must be repeated to-day with much emphasis.

I.—TRANSFORMATION OF ENERGY.

Little is yet known concerning the transformation of energy in gouty individuals, although hypotheses have been earnestly advanced on all sides. The theory runs in this wise: The gouty patient has a "retarded

metabolism." This theory is enunciated most clearly in a scientific form by Bouchard (2), both in his earlier and later writings. It is based on the fact that uric acid accumulates in the tissues of gouty patients, and also on the hypothesis that this uric acid is protected from oxidation to urea by reason of the lessening of the oxidative power of the system. Regarding the extent of the general oxidation in the gouty, only the investigations made by Magnus-Levy (3) on seven patients are available. Magnus-Levy found that the consumption of oxygen by the gouty patient differed in no way from that of the healthy subject (2·41 to 4·33 c.c. O_2 per kilogramme and minute). The constant wide variations of these figures illustrate the well-known law that the values for the consumption of oxygen per minute and kilogramme decrease with increasing size and weight of the patient—that is, with an increasing fatty status. Naturally, in this connection the possibility is not excluded that, as Ebstein (4) believes, certain oxidative processes—perhaps just those which have to do with uric acid—may become markedly affected. This idea finds its analogy in the reaction of the diabetic patient towards carbohydrates and the acetone bodies. One should no longer speak only of a retardation of the metabolism in general.

II.—DECOMPOSITION OF PROTEIN.

The older data connected with the excretion of nitrogen and of uric acid by the gouty may be now neglected. They are of little value for further conclusions, inasmuch as they were obtained without due regard to the protein and calorie intake. Nevertheless, various hypotheses have been based on the values given for these excretions.[1]

The first real basis was furnished by the investigations of von Noorden and L. Vogel (5). With their three patients the excretion of nitrogen remained for a long time much lower than the intake, the difference between these two factors amounting to 1 to 6 grammes per diem. In the case of one patient there were certain days on which the nitrogen output exceeded the nitrogen intake by 1 to 4 grammes. As a rule, the nitrogen output varied although a fixed diet was maintained. The chief results obtained were the daily retention and variation of nitrogenous exchange. The calorie value of the diet was not high enough for protein retention to be expected. In this connection, however, the course of the nitrogenous elimination in renal diseases must be remembered (Vol. II.). The question whether the peculiarities of the nitrogen excretion, and particularly the nitrogen retention, are due to the gout or to a complicating nephritis must remain undecided. As a matter of fact, not a single symptom, such as the condition of the vessels, of the heart and of the urine (which was daily, often several times daily, examined for albumin), pointed to the latter condition.

The tendency of the gouty to retain nitrogen has been corroborated

[1] The older literature is given by von Noorden (6) and by L. Vogel (5).

by other investigators (7). In this confirmation further interesting peculiarities and new questions have arisen.

In his numerous careful observations Magnus-Levy confirmed the fact, already pointed out by Vogel, that the nitrogen retention of the gouty was not continuous, but was interspersed with periods of more marked nitrogen excretion. Magnus-Levy found, during the acute attack, higher values than corresponded to the intake of food ; he attributed these values to the toxogenic decomposition of protein. In this latter view I agree with him. The nature of the toxine in question is still undecided. Uric acid itself might be indicated, for Soetbeer and Ibrahim (8) have shown that subcutaneous injection of uric acid causes an increase in the decomposition of protein, which has throughout the characteristics of a toxic degeneration. Yet it is doubtful whether one is justified in ascribing much value, in the interpretation of gouty processes, to this experiment. We recall the general impression which the gouty patient gives at the time of a severe attack, especially remembering the usual increase of temperature at such periods. Hence we are forced to assume that at this time some type of toxine is acting. The facts which were discovered by Magnus-Levy, and which may later have a great importance in the elaboration of the theory of gout, have been confirmed also by Zagari (9), Kaufmann and Mohr (10), and, in one case, by Brugsch (7).

A period of nitrogen retention follows the increased protein decomposition which is observed during the gouty paroxysm. Magnus-Levy interprets this as a phenomenon of convalescence. The nitrogen retention, which, as is mentioned above, occurs earlier, and of which he himself furnishes a few other examples, may be nothing else than a storing of protein as a result of a previous condition of poor nutrition (outside the hospital), or as a result of overfeeding. This is certainly the condition in a large part of the cases, yet Magnus-Levy had great difficulty in explaining all of his observations on this basis. Such an interpretation was first shown to be correct by the researches of Vogt, and of Kaufmann and Mohr. From a comparison of the nitrogenous equilibrium with that of the phosphorus it was evident that—at least, in part and in certain cases—the nitrogen deficit was conditional upon the temporary accumulation of nitrogenous decomposition products of protein, the nature of which must be further investigated. According to the critical discussions of Kaufmann and Mohr (10), it is very unlikely that the principal part of this could arise from the purin bodies, as Hager, Loewi, and Vogt (11) assume, because the amounts in question (often 2 to 6 grammes nitrogen per diem) are much too large for the purin nitrogen to account for. Only a small part of this nitrogen could be referred to the uric acid or its precursors.

Still more remarkable than the increased protein decomposition which is associated with the acute paroxysm, is the observation that similar periodic variations of protein decomposition also occur in the free intervals and during the course of chronic atypical gout without any other evidence, such as fever, etc., pointing to such a condition. Kaufmann and Mohr noted in two patients, a short time after a mild

acute attack, marked loss of nitrogen (especially in their observation No. 41), although the food contained sufficient nitrogen and calorie values to warrant a retention of nitrogen. A further observation along this line was brought to my notice. We had placed a patient with chronic gout (well-defined tophi, no attack for two months, no complications) upon a constant purin-free diet, in order to test the effect of the addition of meat upon the uric acid excretion. As the protein exchange exhibited unusual characters—the temperature was not increased—the same diet was maintained for a still longer time in order that this question might be further studied. The diet contained about 18 grammes nitrogen, and yielded 45 calories per kilogramme.[1] The diet was commenced two days before the urinary estimations were made.

Day.	*Total Nitrogen.*	*Uric Acid.*
	Gm.	Gm.
3	16·1	0·52
4	16·9	—
5	18·3	0·56
6	20·1	0·77
7	20·9	0·78
8	17·9	0·59
9	17·8	0·51
10	15·9	0·43

Ten weeks later an acute attack appeared. This observation suggests the interpretation that in gout, even during the periods which are free from attacks, specific (?) poisons are present whose injurious influence is more or less evidenced by the amount of protein decomposition, just as is the case in other chronic diseases, such as leuchæmia, pernicious anæmia, exophthalmic goitre, etc.

This peculiar course of the protein metabolism, in support of which not only the excretion of nitrogen, but also the excretion of phosphoric acid, bears witness, and which manifests itself partly by direct association with the paroxysm, and partly, also, during the attack-free periods, is at any rate extremely important. It shows that here a toxic process is at work. The unknown toxines are probably endogenous in nature, as is the case in Graves' disease and also in diabetes mellitus, and not of exogenous origin, as in the infectious diseases. Further than this we cannot go at present.

As has been previously stated, a retention of nitrogen, which is independent of the diet, was the first striking anomaly of the nitrogenous metabolism observed in gout. Von Noorden and Vogel (5), who discovered this condition, and also Schmoll (7), had called attention to the astonishing similarity to the conditions observed in nephritis. This was, indeed, grist to the mill of those who regarded the disease of the

[1] It was only possible to once examine the fæces. On this day they contained 1·8 grammes nitrogen. There was a daily action. They appeared to be normal. The daily diet consisted of two eggs, 2½ litres of milk, 200 grammes of white bread, 120 grammes of butter, and one apple. These substances were not analyzed, but, owing to their simple composition, this omission is not of importance.

kidney as the cause of gout, and especially of the retention of uric acid. In these cases, however, the clinical signs of nephritis were not evident. It was justly emphasized by others that the absence of albuminuria did not exclude the presence of a nephritis (contracted kidney). These same findings were also observed in other cases, which were published later by Magnus-Levy, Leber, Kaufmann and Mohr, Vogt, and others. It would, indeed, be very remarkable if all of these numerous patients were, notwithstanding, suffering with a severe kidney disease without albuminuria or some other symptom indicating the condition to clinically experienced observers. Moreover, the early stages of interstitial nephritis, regarding which this question, at best, could be raised, are never accompanied by such nitrogen retentions. I, personally, have carefully excluded from the researches carried out in my clinic on the metabolism of gout [Kraus, Leber, Kaufmann and Mohr (7)] those patients in whom the condition of the urine, heart, arteries, blood-pressure, etc., suggested renal changes. Others seem to have followed the same plan. Naturally, owing to the frequent sequence of gout and contracted kidney, nephritis often exerts an influence on the nitrogenous metabolism of the gouty. I believe that we are now in a position to say that arthritis urica itself, without the co-operation of nephritis, may disturb the normal equilibrium of the nitrogen excretion. This is, however, not always the case, for absolutely normal relations are sometimes present, according to the figures of Magnus-Levy, Kaufmann and Mohr, Brugsch and Soetbeer (12).

One should no longer speak of a "retardation of the protein metabolism." This idea is frequently advocated in the older writings, and plays a great part in the theory of E. Pfeiffer (13). On the other hand, the question has been recently raised whether or not the nuclein metabolism is especially retarded. To this end the work of Schmoll, and more particularly of Vogt, Kaufmann and Mohr, and Reach (7) is directed. The investigations should serve to decide the question as to how the gouty patient reacts to the intake of nuclein. Vogt's patient promptly excreted phosphoric acid on a diet containing nuclein, while the nitrogen was, to a great extent, retained in the body and gradually excreted later. How uncertain it is to draw general, and at the same time valid, conclusions regarding the nuclein metabolism of the gouty from such experiments is indicated by the similar investigations of Kaufmann and Mohr (10). They show, on the basis of their extensive research material, that the comparison of the nitrogen and phosphoric acid equilibrium is not generally applicable to the solution of this question. More important, it seems to me, is the establishing of the fact that gouty patients, after the addition of uric acid forming materials (nuclein) to the diet, remarkably often exhibit retarded and lessened uric acid output when compared with healthy subjects under similar conditions [Vogt, Kaufmann and Mohr, Reach, and Soetbeer]. According to the investigations of Soetbeer, this fact is very neatly shown if the hourly as well as the daily curve of the uric acid excretion is studied. Although individual observations show other results [Weintraud, Schmoll (15)], yet, according to the results recently obtained by reliable methods, decrease (or slowing) of the uric acid excretion (as compared with that of the

healthy subject) seems to be the rule, while a promptly increased output appears to be the exception. This is certainly an extremely important fact, and one to which frequent reference will be made. It indicates qualitative and quantitative changes in the breaking-down of nuclein, and especially of its purin nucleus. One should not, in this connection, jump to the conclusion of renal insufficiency, and endeavour, by this means, to explain the inadequate elimination of uric acid. For, in the first place, in all the patients who were subjects of investigation no signs of nephritis were present, and, secondly, patients with severe kidney lesions do not react to uric acid forming food as well as do healthy subjects, but still, they react much better than do the gouty patients.

III.—THE DIGESTIVE ORGANS.

1. General Relations.

Some cases of gout are characterized by disturbances of the gastro-intestinal functions. These disorders are usually manifested by constipation and flatulence. In other cases, fortunately rare, a tendency to severe but controllable diarrhœa is observed. Both conditions, associated with nausea and anorexia, are often precursors of the gouty paroxysm, so that the impression is given that these conditions have to do with the development of the acute attack. Many authors—as, for instance, Grube (16), and, with greater reserve, Magnus-Levy and Minkowski (1)—attach much importance to this temporary relationship and to the etiological connection derived from it. I have for many years very carefully followed this question in at least thirty cases who have suffered with regular typical attacks of gout. In these, with very few exceptions, the acute attack developed without any sort of a dyspeptic precursor. In the first place, along with the appearance of the gouty paroxysm, certain disturbances were evident which differed neither in intensity and duration, nor in their characteristics, from those disorders which are observed in every irregularity of the general health, and especially in acute febrile conditions. On the other hand, it is not to be denied that gouty subjects suffer from many gastric disorders. The gouty individual has sufficient occasion to contract such gastro-intestinal disturbances. Apart from the medicinal treatment, he is also dietetically maltreated, because this or that substance is forbidden—usually without rhyme or reason—so that a condition of one-sided nutrition arises which carries in its train digestive disturbances, especially an atonic condition of the bowel. Mention must also be made of those influences which are prejudicial to the digestive functions. Among these may be cited the courses of alkalis (sodium bicarbonate, uricedin) and of alkaline mineral waters (Fachingen, Neuenahr, Vichy) which it is customary to prescribe. Many gouty patients owe their gastric disorders to the same causes which are at work in other patients who suffer from stomach trouble. On account of the frequency with which digestive disturbances of the most variable

kind arise, and owing to the tendency of so many patients to react to every irregularity of the general health by disorders of the digestive functions, the most careful critical inquiry is necessary in this connection. One does not seem to be warranted in drawing far-reaching theoretical conclusions regarding the etiological interpretation of digestive disturbances in gout from the clinical facts, as Grube (16) and, recently, Falkenstein (17), have done in reviving the old hypotheses.

2. The Saliva.

Edinger (18), whom we must thank for his valuable researches on the importance of the sulpho-cyanates to the animal organism, asserts that, in the subjects of the "uratic diathesis," the sulpho-cyanide reaction of the saliva cannot be obtained. After the administration of the sulpho-cyanates to such cases the reaction is positive, but it disappears in about three weeks. I was unable to find that the lack of such compounds in the saliva was typical and regular. I treated the saliva of four gouty patients with ferric chloride during my consultation hours. Thrice the reaction was positive, once it was negative. This latter patient had just finished a course of mercurial treatment, which regularly occasions a negative sulpho-cyanate reaction in the saliva for some time.

For the excretion of uric acid in the saliva, see Index.

3. Secretion of Hydrochloric Acid in the Stomach.

Magnus-Levy (3) observed that while the HCl production was decreased during severe attacks, it was normal in milder attacks. In chronic cases with moderate degrees of acidity free HCl was usually absent; Magnus-Levy attributed this either to the chronicity of the gouty condition, or to alcoholism. Grube (16) in seven cases of severe chronic gout failed to detect HCl four times. I found in four patients no free HCl during the acute attack (a phenomenon which other febrile conditions likewise show). Between the attacks—as I have reported previously—the secretion varied considerably; even hyperacidity sometimes occurred. In the course of the last two years I have devoted special attention to the question with reference to Falkenstein's work.[1] I had the opportunity to obtain the following figures in the cases of six robust

[1] Falkenstein believes that diminished HCl secretion is the primary trouble in gout, and that, owing to this, the decomposition of nuclein, and especially the oxidation of uric acid to urea and oxalic acid, is restricted. As a result the system, according to Falkenstein, becomes overloaded with uric acid, and gout follows. Administration of HCl facilitates the decomposition of uric acid, and lessens the uric acid output in the urine, so that this is a natural and unfailing therapeutic agent in gout. I will not go into the deductions of Falkenstein (19), which stand in marked contrast to the physiological facts as we at present are able to interpret them. However, the following facts may be advanced against his hypothesis: (1) There are numerous pathological conditions in which HCl is absent from the stomach for months and years without a condition of gout arising. (2) There are numerous gouty patients who excrete normal amounts of HCl. (3) When the largest permissible doses of HCl are given to persons who are under the same dietary regulations, the excretion of uric acid is not diminished, or only temporarily so (for one to two days). In such cases a slight transient increase occurs (personal investigations).

middle-aged, non-alcoholic, gouty subjects. The stomach contents were examined after test breakfasts, which consisted of four crackers and 8 to 16 ounces of tea. The contents were removed from the stomach thirty-five to forty minutes after the beginning of the breakfast.

Case.	*Total Acidity.*	*Free HCl.*
	Per Cent.	Per Cent.
1	0·24	0·15
2*a*	0·27	0·15
2*b*	0·24	0·16
2*c*	0·29	0·20
3	0·18	0·08
4	0·30	0·18
5	0·25	0·12
6	0·16	—

Deficient HCl excretion does not appear to be characteristic of gout. When such a condition does obtain, it must be considered as a complication due to gastritis of general inanition.

4. Intestinal Putrefaction.

The intestinal putrefaction of protein may be markedly increased in acute cases. Magnus-Levy (3) often found enormous amounts of indican in the urine in acute attacks. By oxidation of this chromogen a red pigment (indigo red ?) was frequently observed, which was easily soluble in amyl alcohol. The subjects of chronic gout excrete abnormal quantities of chromogen, frequently over long periods. The observations of Oechsner de Coninck (20), and those made in my wards, confirm these statements. Yet typical severe gouty attacks occurred in which only a normal indican reaction was obtainable. Two patients of Grossmann showed an increased indican reaction so long as they were under the influence of a meat diet. On changing to a purin-free diet, the indican quickly disappeared.

5. Absorption of Food.

The results of the experiments on the assimilation capacity of the gouty are very remarkable. The first investigations on the metabolism in gout, which Vogel carried out under my direction, showed a marked loss of nitrogen in the fæces, as the fæcal nitrogen was less than 10 per cent. of the nitrogen of the food in only two out of seven cases. Thirty experiments were made on the assimilation of sixteen gouty patients by Vogel, Schmoll, Magnus-Levy, Vogt, Kaufmann and Mohr (5 and 7), if we disregard those cases in which medicinal agents or large amounts of nuclein or thymus were administered. In all of the cases, the food was of such composition that not more than 8 to 10 per cent. of the nitrogen ought to have been lost. Only five of the patients showed good absorp-

tive functions—that is to say, the nitrogen loss in these cases did not exceed 8 per cent. of the nitrogen intake in ten experimental periods.[1]

In four patients (four experimental periods), the nitrogen loss lay between 8 and 10 per cent.; this cannot be regarded as exactly pathological. These normal, or nearly normal, values are met with during the gouty paroxysm as well as in the intervals between the attacks.

In ten patients (sixteen experimental periods), the nitrogen was 10 to 16 per cent. Among these there were nine periods in which the loss was more than 12 per cent. Several of these patients excreted much less fæcal nitrogen at other times. The greater number of the high values appeared during the gouty attack, although amounts which were pathological occurred in the intervals, especially in chronic atypical gout.

Inasmuch as Vogel was able to prove that, along with the abnormal nitrogen values, a normal absorption of fat obtained (loss of fat in the fæces between 5·01 and 7·32 per cent. of the intake), we concluded that the high values for nitrogen were not the expression of a poorer absorptive power of the intestine, but rather that they yielded evidence in favour of an especially abundant secretion of intestinal juice, or, in other words, that the absorption of nitrogen from the intestinal canal was not too small, but that the excretion of nitrogen into this region was unusually large. A similar condition occurs in nephritis. Von Noorden and Ritter (22) found a low excretion of fat, and frequently a very marked excretion of nitrogen, in the fæces of nephritic patients. The origin of this increase in fæcal nitrogen is unknown. Petrén (23) examined the fæces for xanthin bases, and found the daily amount in one gouty patient normal—that is, 62 milligrammes (in healthy subjects the excretion ranges between 50 and 100 milligrammes (average of 68 milligrammes).

Petrén's method was not entirely free from objections. After the fæces had been treated with sulphuric acid, he precipitated the bases with ammoniacal silver solution. By this procedure a portion of the purin bases would escape detection. New investigations along this line are much to be desired. In this work one must make use of the better methods of Walker Hall or of M. Krüger and A. Schittenhelm (24), which have as yet not been applied to the fæces of the gouty. According to Walker Hall and Schittenhelm, the fæcal purins chiefly arise from the nuclein material of the cells of the alimentary tract, but partly also from the nuclein of the bacteria.

Walker Hall observed that administration of thymus and pancreas to healthy subjects resulted in a large increase of fæcal purin nitrogen. Kaufmann and Mohr found that a large intake of thymus by a gouty individual was followed by an increased nitrogen and P_2O_5 output in the fæces, but that the rate of assimilation was not much less than that of the healthy controls.

The exact origin of the increase in the high fæcal nitrogen loss of the gouty is still undetermined. Perhaps the phenomenon is related to the

[1] The experimental results are tabulated in Kaufmann and Mohr's paper (7). To these should be added two cases with good absorption—that is, nitrogen loss below 8 per cent. (in chronic gout and in the intervals between attacks of gout)—and also five cases with unsatisfactory absorption (nitrogen loss between 9·5 and 12·4 per cent.). These latter cases were all observed in the acute stage [T. Brugsch (7)].

abnormalities in the protein decomposition (see above), to which Magnus-Levy has already referred.

Above all, it must be ascertained if the bacterial content of the fæces of the gouty is abnormally high. The methods which are most applicable in this work are either that of Strasburger or that of A. Schittenhelm and C. Tollens (25). If this be the case, then a somewhat higher purin-base content of the fæces would not be surprising, since a certain proportion of the purin nitrogen is definitely bacterial in origin.

IV.—URIC ACID IN GOUTY CONDITIONS.

1. General.

Although some of the already discussed anomalies of the metabolism in gout may contribute more largely to the solution of the etiological factors concerned than is at present admitted, the chief interest to-day is centred upon the formation and excretion of uric acid. If one disregards the purely theoretical discussions of earlier periods, the investigations on the relation of uric acid to gout extend back only to Sir A. Garrod. His urine and blood analyses showed that the gouty patient excretes less uric acid on an average than the healthy subject; frequently only traces were demonstrable. The decrease is most marked before and during the attack; later the excretion again approaches normal values. The uric acid in the blood is increased at the time when the decrease in the urine is apparent.

Upon these points were based Garrod's historically important theory of gout (26). The kidneys of the gouty do not excrete uric acid as quickly as it is formed. Under the influence of certain, but very different, conditions this power of uric acid elimination is markedly reduced. As a result, there is an accumulation of uric acid in the blood. When the uric acid reaches a certain percentage, an acute attack follows. Uric acid is vicariously excreted into the tissues, where it may be later oxidized and dissolved by the aid of inflammatory processes. In this way the blood rids itself of uric acid. For a certain time the uric acid formation and excretion are again maintained within approximately the same limits until new disturbances of elimination arise. In chronic irregular gout the uric acid excretion must be continuously and more uniformly decreased; often only traces of uric acid are to be found.

In passing to the exact investigations of recent times, the researches of Lehmann, Ranke, Braun, Lécorché, Cantani, Bartels, and others (27), must be disregarded. They all confirmed the data of Garrod, but unfortunately, like Garrod, they employed the method of Heintz, which, as we now know, yields unreliable results. It is to be regretted that so much legitimate work of deserving men should be considered fruitless on account of late recognition of the faults in the methods adopted.

It is now customary to consider that uric acid arises from—

1. The nuclein substances of the degenerating body cells, and, as

Burian (28) has recently shown, the hypoxanthin of muscle tissues. The purin nucleus, both of the nuclein and of the muscle hypoxanthin, is probably formed in the body itself. The mode of synthesis is not known. That portion of the uric acid which arises from this source within the body and appears in the excretions is termed, according to the precedent of Burian and Schur, endogenous uric acid. To this should be added the synthetically-formed uric acid. Direct synthetic uric acid formation plays, according to Wiener (29), who has advocated this most actively, only a very subordinate rôle in the mammalian organism. Recently this point has been altogether opposed by Burian (28).

2. The nuclein substances and purin bases of the food. This portion is called exogenous uric acid.

In the formative processes of uric acid the following ferments play an active part :

(*a*) A *nuclease*, which is able to split up nucleinic acid, so that the purin bases, especially guanin and adenin, which are contained therein, are set free [Schittenhelm (30)].

(*b*) A *hydrolytic ferment*, which acts by disamidation, and converts guanin into xanthin, and adenin into hypoxanthin.[1]

(*c*) An *oxidase* (xanthin oxidase), which converts xanthin and hypoxanthin into uric acid [Spitzer, Wiener, Schittenhelm, Burian (32)].

Whether there are other influences at work in this process is still uncertain. The principal end-product of the breaking-down process is uric acid. Uric acid is present in excess in the blood, urine, and the gouty deposits, while in tissue extracts the quantity of purin bases exceeds that of the uric acid, which then occurs only in traces. However, a portion of the bases always escapes the action of the oxidizing ferment, so that uric acid is universally accompanied by other purin derivatives, especially in the urine. Rather wide conclusions have been drawn from the mass relations of the urinary xanthin bases on the one hand, and the urinary uric acid on the other, by Kolisch (40). The hypotheses he advanced did not throw any light on the pathogenesis of gouty processes.

Only a fraction of the endogenous and exogenous end-products of purin metabolism appear in the urine ; the remainder is further decomposed. In confirmation of the old feeding experiments with uric acid, the uric acid destroying power of the tissues has been shown by numerous direct investigations [Wiener, G. Ascoli, Schittenhelm, Burian, and others (33)]. The kidneys, especially, possess this power in a high degree [Wiener, Schittenhelm]. The isolation of an active solution of a uricolytic ferment has recently been achieved [Schittenhelm, Wiener (34)].

The numerical relation between the formation and the excretion of endogenous end-products of purin metabolism is unknown. We know only the amount of such excretion, which is 100 to 200 milligrammes of

[1] Regarding this ferment a discussion has arisen between Schittenhelm (30A) on the one hand, and Jones, Partridge, and Winternitz (30B) on the other hand. The latter believe that they have detected two different ferments, guanase and adenase, which act as disamidators of guanin or adenin. Schittenhelm (31) seems, however, to have furnished the conclusive proof that it is a question of only one ferment, towards which guanin is, however, more resistant than adenin.

endogenous purin nitrogen, corresponding to 300 to 600 milligrammes of uric acid in a grown man on a purin-free diet. As has been mentioned in Vol. I., this value is influenced by the personal factor. It is, however, extremely constant for single individuals [Burian and Schur, Walker Hall, Sivén, Kaufmann and Mohr, Rockwood (35)]. Whether persons who excrete large amounts of endogenous uric acid form more purin bodies or destroy less of that formed cannot at the present time be differentiated.

In regard to the exogenous urinary purin, the question can be better answered. About 50 per cent. of the purin bodies which, according to theoretical calculations, may arise from the nuclein substances, etc., of the ordinary food-stuffs reappear in the urine. The largest part of this (four-fifths to seven-eighths) is found as uric acid, while a small part (one-eighth to one-fifth) is excreted as alloxur bases [Burian and Schur, Walker Hall (36)]. Kaufmann and Mohr, as well as Magnus-Levy, justly call attention to the fact that individual factors also play a rôle in this connection. The value of 50 per cent. given above must be regarded only as the average figure. Although further investigation of a large number of individuals is still necessary to establish the true physiological limits of this value, which I estimate, according to my own determinations, as 40 to 55 per cent., yet it is indeed remarkable, and doubtless legitimate, that about 50 per cent. should universally prevail as the average value. This was shown, for instance, in the recent investigations of von Rzentkowski and of B. Bloch (36A).

2. Uric Acid Excretion in the Gouty under Ordinary Non-restricted Diet.

When the wide variations of this as well as of other important factors are considered, it is not surprising that the peculiarities of the uric acid excretion of the gouty were so late in being recognised. As my treatise on "The Pathology of Metabolism" appeared twelve years ago, I was then obliged to write that a typical course of the uric acid excretion did not obtain in arthritis urica. I pointed out that this might be due to the fact that high and low values appeared both in acute and chronic gout so irregularly as not to permit of the recognition of any special relations.

To a certain extent the same thing is true to-day. When the series of figures, which have been obtained without any systematic regard to the diet, are reviewed, it will be seen that the values vary within the limits of healthy subjects (37). No one can decide from single, or even from a large number of uric acid determinations, whether or not he has to do with a case of gout. If the average values obtained in health are compared with those observed in gout, almost identical figures are obtained. The peculiarities which occur during the acute attack are discussed later.

Fully recognising these facts, Pfeiffer (38) endeavoured to take a new standpoint of the uric acid question in gout by advancing the concep-

tion of "easily" and "difficultly" separable uric acid. As "easily separable" he regards the urinary uric acid which is deposited on filtering through a "uric acid filter." This uric acid should be increased in gout at the expense of the "difficultly separable" uric acid. This analytical method, for which a pre-eminent diagnostic value was claimed, has long been regarded as inadmissible, and to-day no one speaks of the theory which is based upon it (39). These questions have at the present time no importance except as regards the origin and solution of uric acid renal calculi—that is to say, as regards a disease which is very remote from gout (see chapter on Drink Cures).

3. Relation of Uric Acid to Purin Bases.

A further peculiarity, to which Kolisch (40) referred, has likewise not been confirmed. Kolisch regarded the kidney as the seat of uric acid formation, the uric acid arising from the other alloxur bodies through the specific action of the kidney epithelium. This process is disturbed both in gout and in nephritis, and the alloxur bases of the urine are consequently increased in gout, while the uric acid is lessened both absolutely and relatively—that is, in relation to the alloxur bases. Moreover, the metabolism of the gouty patient furnishes cause for increased formation of alloxur bases. Kolisch, therefore, took exception to the name uric acid diathesis, and regarded gout as an alloxur diathesis.

The figures upon which Kolisch based his theory were obtained by the Krüger-Wulff method. This method gave inexact results, and Kolisch's view fell to the ground when newer and more reliable methods showed that in gouty subjects the normal relations of uric acid and the purin bodies were unaltered. The following examples illustrate this point :

Author.	*Purin Nitrogen.*	*Uric Acid Nitrogen.*	*Uric Acid N. / Purin Base N.*	*Duration of Experiment.*	*Remarks.*	
Kaufmann and Mohr :	Gm.	Gm.	Gm.	Days.		
Case 20	0·149	0·126	5·5	—	Interval	Purin-free diet.
,, 21	0·140	0·130	14·0	6	,,	
,, 22	0·204	0·165	4·2	3	,,	
,, 23	0·201	0·164	4·4	4	Acute gout	
,, 24	0·182	0·141	4·4	2	,,	
,, 25	0·161	0·131	4·4	6	,,	
Walker Hall:						
Case 4	0·064	0·057	8·1	6	Chronic gout	
,, 5	0·071	0·063	10·5	5	,,	
Average	0·146	0·122	5·1	—	—	
Kaufmann and Mohr :						
Case 41	0·301	0·261	6·5	4	Acute gout	Purin-holding food.
,, 42	0·240	0·214	8·2	3	,,	
,, 43	0·230	0·211	11·0	2	,,	
,, 39	0·576	0·294	1·1	4	Chronic gout	
Benjamin :						
Case 33	0·095	0·094	6·8	1	,,	
Cases 34-37	0·436	0·374	6·0	4	,,	

As a normal average for a purin-free diet (first part of the table) we find 0·12 to 0·20 gramme purin nitrogen and 0·10 to 0·18 gramme uric acid nitrogen. The relation of uric acid nitrogen to base nitrogen varies between four and eight to one. Only two values shown in the above table point to a much narrower relation than these normal quotients.

Exact consideration of the recently obtained information regarding the physiological uric acid excretion has disclosed a few further peculiarities which obtain in gout. Unfortunately, the number of available investigations is still very small, so that much is left for the future to determine.

4. Uric Acid Excretion of the Gouty on Purin-free Diet.

The study of the uric acid excretion on a purin-free diet is of especial value.

Author.	*Purin Nitrogen.*	*Uric Acid.*	*Average of Number of Days.*	*Stage of the Disease.*
	Gm.	Gm.		
Laquer	—	0·213	6	Chronic.
Strauss	—	0·362	6	,,
Grossmann	—	0·752	3	Acute attack.
	—	0·619	5	,,
	—	0·522	6	,,
Soetbeer	—	0·351	1	Slight acute attack.
	—	0·279	3	Chronic.
	—	0·420	1	,,
	—	0·396	3	,,
	—	0·302	2	Attack, without fever.
Brugsch	—	1·07	2	Attack.
	—	0·57	10	Interval.
	—	0·57	8	Attack.
	—	0·34	11	Interval.
	0·25	—	10	Attack.
	0·19	—	14	Interval.
	0·18	—	11	Attack.
	0·12	—	6	Interval.
	0·21	—	8	Attack.
	0·16	—	4	Interval.
Von Noorden and Schliep	—	0·462	4	Chronic.
Von Noorden (1) ..	—	0·310	5	,,
Von Noorden (2) ..	—	0·321	4	,,
Von Noorden (3A) ..	—	0·675	2	Attack.
Von Noorden (3B) ..	—	0·397	2	Interval.
Von Noorden (3C) ..	—	0·402	3	,, (one year later).
Schliep (1) ..	—	0·396	5	,,
Schliep (2A) ..	—	0·416	3	Chronic.
Schliep (2B) ..	—	0·415	11	,,
Schliep (3) ..	—	0·346	12	,,
Schliep (4) ..	—	0·449	4	,,
Schliep (5) ..	—	0·578	3	,,
Schliep (6) ..	—	0·393	5	,,
Schliep (7) ..	—	0·522	7	Acute attack.
Schliep (8) ..	—	0·501	5	,,
Kaufmann and Mohr	0·140	0·391	6	Chronic.
	0·139	0·398	3	The same patient four weeks later.

For further examples, consult the works of Futcher, Chalmers Watson, W. Bain, A. T. Laird, Walker Hall (73, 97, 119).

A glance at the table will reveal the fact that the values chiefly lie within normal limits. Yet these values, apart from those obtained during the acute paroxysms, approximate more nearly the lower than the upper limits.

Unfortunately, only a few investigations have been continued for long periods. Kaufmann and Mohr observed during the attack-free periods somewhat greater variations than normally occur on a purin-free diet. In another case which was investigated three months after the last and six weeks before the next attack I also observed marked variations in the excretion of endogenous uric acid. The determinations commenced on the fifth day of the purin-free diet.

Day.	*Uric Acid.* Gm.	*Day.*	*Uric Acid.* Gm.
5	0·521	9	0·487
6	0·328	10	0·561
7	0·361	11	0·472
8	0·298	12	0·444

Still greater variations were present in the cases of Brugsch, although all of his patients were observed in the periods showing frequent severe and mild attacks, which both previously and subsequently influence the excretion of uric acid.

5. Uric Acid Excretion of the Gouty on Purin-containing Diet.

Variations of the Excretion on a Constant Diet.

Garrod, as is known, taught that the excretion of uric acid is always markedly lessened in chronic atypical gout. This error arose from the inadequacy of the method employed, and to the fact, further, that patients with chronic gout eat, as a rule, little meat. If, however, a gouty individual takes as much meat and other purin-containing substances as a healthy subject, then the uric acid figures do not differ essentially the one from the other. In spite of this, certain amounts of uric acid may, in the sense of Garrod, remain behind in the body ; for a uric acid value which differs from the normal daily average only by a few centigrammes will always appear normal, although the daily repetition of the same insignificant retention may result in the retention of considerable amounts of uric acid as time goes on. These amounts would be sufficiently large to explain the increased uric acid content of the blood and the uric acid deposition in the tophi. As a matter of fact, a few observations point to the possibility that a certain degree of retention may obtain in spite of an apparently normal uric acid elimination. When the patients were kept on absolutely the same diet, I occasionally observed a sudden and marked increase of uric acid on one or two or three successive days. This increase amounted to 200 to 250 milligrammes. In the two cases which are presented in the following table, and which were observed in the attack-free intervals, the daily diet contained 400 grammes (raw weight) of beef along with purin-free food-substances. The uric acid estimations began on the third day of this diet.

Day.	Uric Acid.	
	Case 1.	Case 2.
	Gm.	Gm.
3	0·61	0·72
4	0·58	0·76
5	0·59	0·68
6	0·78	0·64
7	0·80	0·82
8	0·65	0·86
9	—	0·65
10	—	0·77

It is not impossible that dissimilar purin nitrogen content of the meat was partially responsible for the above differences, yet the variations are too great to permit of the assumption that this is the only cause. This course of excretion agrees throughout with what has been said regarding endogenous uric acid. The nitrogen values vary markedly, inasmuch as the intake of purin-free food-substances was left to the individual inclination of the patient.

I regard as very important the spontaneous variations of the uric acid excretion which arise in the course of the attack-free intervals, because they suggest the line of treatment necessary. The indication is to induce this condition, which at times appears of itself, and which evidently leads to a certain degree of purification of the blood as regards uric acid. Only a few substances are known to exert definite influences on the uric acid excretion. This is not the place to discuss these therapeutic points of view in detail, although a few especially important influences ought to be mentioned (45).

Alkalis have little action on the uric acid output. They may slightly lessen the excretion; they rarely induce an actual increase (see Drink Cures).

Author.	Examples.	Duration.	Uric Acid.	Remarks.
			Gm.	
Laquer ..	Endogenous uric acid	Average of 6 days	0·213	—
	Same food + 1 bottle Fachinger water and 15 gm. sodium bicarbonate	Average of 3 days	0·240	—
Von Noorden	Fixed purin-free diet:			
	Without alkali	3 days	0·641	Gout and slight diabetes.
	With 6 gm. sodium bicarbonate	2 ,,	0·580	
	Without alkali	2 ,,	0·650	
	Purin-free food:			
	Without alkali	2 ,,	0·652	Gout with continuous slight feverless attacks.
	With 6 gm. sodium bicarbonate	2 ,,	0·635	
	Purin-free food + 150 gm. beef (raw weight):			
	Without alkali	4 ,,	0·555	Gout; continuous slight feverless attacks.
	With 6 gm. sodium bicarbonate + 1 bottle Fachinger	8 ,,	0·545	
	Without alkali	5 ,,	0·566	

Author.	*Without Alkali.*	*With Alkali.*	
	Gm.	Gm.	Gm.
W. His	0·49	0·43	12 sodium bicarbonate.
	0·42	0·46	12 ,, ,,
	0·57	0·55	12 ,, ,,
	0·46	0·41	12 ,, ,,
	0·46	0·40	12 ,, ,,
	0·58	0·26	0·2–1 lithium carbonate.
	0·46	0·41	0·2–1 ,, ,,
	0·46	0·43	0·2–1 ,, ,,
	0·62	0·46	0·2–1 ,, ,,
	0·65	0·60	0·2–1 ,, ,,
	0·27	0·23	0·2–1 ,, ,,
	0·57	0·42	0·2–1 ,, ,,
	0·58	0·38	Fachinger salts (Sandow).

Sodium salicylate causes a marked transitory increase in the uric acid excretion, even when purin-free food has been continued for several years [Walker Hall (44)].

Alcohol does not act uniformly in gout (45). In a few cases lowering of the uric acid elimination was observed—as, for instance, by Leber (preceding period 0·212 gramme uric acid, alcohol period 0·201 gramme, subsequent period 0·266 gramme). Still more marked was the result in the case of a fifty-year-old gouty patient who was afflicted with extensive tophi, but was, at the time of observation, free from an attack. I allowed him to take, along with a purin-free diet, 80 c.c. of cognac daily during the four days of the alcohol period.

	Uric Acid. Gm.
Preceding period (four days)	0·405
Alcohol period (four days)	0·281
Subsequent period (two days)	0·412

Escheburg investigated this point in three gouty patients. Alcohol produced no effect on an old woman, who showed extremely low uric acid values. The uric acid excretion of an old man in the stage of chronic inactive gout decreased under the influence of 50 grammes of alcohol from 0·18 to 0·24 gramme (on a meat-free diet) to 0·15 to 0·20 gramme. In the case of a fifty-five-year-old gouty subject, who received 150 grammes of meat in addition to his purin-free diet, the uric acid excretion increased after the use of 50 grammes of alcohol from 0·65 gramme to 1·08 grammes (four-day period). Whether this increase is traceable to the alcohol remains uncertain. Moreover, this patient showed remarkably large variations in his uric acid excretion (on a purin-free diet 0·24 to 0·70 gramme as the average values of periods of several days).

Weak saline mineral waters very frequently cause an increased excretion of uric acid. Kissingen, Rakoczy, and Homburg (Elizabeth Spring) waters were investigated in this connection (see Drink Cures).

All of the patients who were examined in this regard were in the attack-free stage of gout. The sudden increased excretion of uric acid,

which appears in part spontaneously, and in part after use of mineral waters, etc., has all of the characteristics of a critical excretion, and seems to indicate a preceding retention. These increased excretions appeared without any sort of a change being evident in the external symptoms of the patient. If one has not earlier noticed this spontaneous increase of the uric acid excretion which occurs in the course of chronic gout, then the failure to do so is probably traceable to the fact that he has not observed the patients long enough under absolutely the same dietary conditions. Or possibly the patients were allowed too much variety. As a result of this the uric acid excretion fluctuates more or less, and the natural independent variations thus escape notice.

It must be the object of still further investigation to decide whether the fluctuations of the uric acid excretion are constantly associated with the previously mentioned variations in the excretion of nitrogen.

6. Uric Acid Excretion after the Addition of Purins to the Dietary.

A further peculiarity is noted in the behaviour of uric acid following the administration of purin-containing food. Although a few observations on this point were previously known, Soetbeer recently emphasized the fact that the increase observed in the uric acid excretion of the gouty after addition of purin substances to the diet appeared more slowly, and did not reach such high values as in the healthy subject. This increase was not found in every case and in every stage of the disease, although it was frequent enough to show that in the gouty tissues certain obstacles are raised against the excretion of uric acid.

The work of Kaufmann and Mohr, Soetbeer, and Brugsch gives absolutely conclusive proof in regard to this point. The results of personal observations, which are given in the following table, complete the above findings. The largest part of these investigations was conducted by my assistant, Schliep. After the endogenous uric acid content of the urine was determined, the patients received for two to three days a certain amount of fillet of beef, which was of such composition that, for every 100 grammes of raw weight, 0·03 gramme of purin nitrogen (the equivalent of 0·09 gramme of uric acid) should be excreted in the urine both on the meat days and on the first one to two purin-free days of the subsequent period. The purin-base nitrogen may be neglected, inasmuch as the general consensus of opinion is that addition of meat increases the uric acid to a considerable extent, and the purin bases only to a very insignificant degree (see table, p. 664).

The table, whose subject-matter far exceeds that published elsewhere up to the present time, shows that great differences exist in the reaction of gouty patients to intake of purin-containing substances. Very often the excretion was all that could be desired. Such observations have been made by Weintraud, Magnus-Levy, Rommel (45). The point now remains to determine the conditions which retard or increase the uric acid elimination. With the reservation that many supplementary in-

vestigations are still necessary, the following points seem to me to be evident from what is known at the present time :

1. There are spontaneous periods of sufficient and periods of deficient uric acid excretion.

Case.	*From the Addition of Meat—*			*Remarks.*
	Expected Uric Acid.	Realized Uric Acid.	Per Cent.	
	Gm.	Gm.		
1	0·72	0·36	50	Chronic.
2A	1·44	0·71	49	Interval.
2B	1·08	0·20	19	Before attack.
2C	0·72	0·30	41	Two weeks later.
3	1·08	0·84	80	Chronic.
4	0·72	0·11	15	Gouty joints.
5	0·72	0·42	58	Chronic (no acute attack for three months).
6	0·72	0·78	100	Tophi (no acute attack for years).
7	0·72	0·27	37	Continuous slight attacks.
8	0·72	—	—	Continuous slight attacks.
9A	0·72	0·28	40	Continuous slight attacks.
9B	0·46	0·37	80	One week later (slighter purin addition).
10A	0·72	0·35	48	Chronic (for six months no attack).
10B	0·72	0·68	94	Eighteen months later : Between period purin-poor food without any special treatment ; no new attacks.
11A	0·72	0·62	88	No attack for two years.
11B	0·72	0·24	33	Eighteen months later : Two months before the estimations severe attack.
12	0·72	0·14	20	Marked attack.
13	0·72	0·19	26	Just after attack ; swelling not yet disappeared.

2. The excretion is markedly retarded and diminished during the time of the gouty paroxysm (periods of frequent attacks, Nos. 2B, 4, 7, 8, 9A).

3. The reaction to the intake of smaller amounts of purin bodies may be good, while it is poor towards larger amounts (9A and 9B).

4. Longer administration of a diet poor in purin bodies seems to increase the power of eliminating uric acid (10A and 10B).

On the basis of these points of view von Noorden and L. Schliep proposed to determine in every case of gout the power of excreting the purin material which was given the patient, and to calculate from this the amount of purin-containing food-substances (especially meat) which should be allowed to the individual patients (see also 44). This is practically a determination of the patient's tolerance, similar to that which one employs in estimating the amount of carbohydrate for a diabetic. As meat does not contain absolutely uniform amounts of purin material, it would, it is true, be theoretically more correct to use weighed amounts of meat extract or of nuclein for the tolerance tests. In purely scientific investigations one must in the future, following the suggestion of B. Bloch,

adopt this plan. However, for practical purposes the tolerance determinations with meat are quite sufficient.

Whoever ascribes to the kidney the primary cause of uric acid retention in the gouty (see below) will explain the retardation of uric acid excretion after intake of purin by the assumption of an anatomical lesion in the kidney, or at least of a functional insufficiency of this organ. This is not tenable, because nephritic patients react, even in the later stages of disease, more promptly to addition of purin substances than do the gouty. A few of the figures which my assistant, Schliep, obtained are reported in the section on Nephritis in Vol. II.

7. The Uric Acid Excretion during the Acute Attack of Gout.

Among the earlier voluminous and somewhat confused data on the uric acid excretion during the gouty attack, those of Pfeiffer (46) are conspicuous as the first investigations which led to certain results. He asserted emphatically and repeatedly that the uric acid of the urine was by no means lessened, as Garrod advocated, but was frequently markedly increased, as in the paroxysmal uric acid shower. Similar evidence in favour of this view was found in the series of figures which Ebstein and Sprague and Vogel (47) published soon afterwards. The deductions made by Pfeiffer from his ascertained facts have not gained a wide acceptance. Through the investigations of His and of Magnus-Levy (49) the uric acid shower observed in gouty attacks has received its first recognition. Although in these experiments sufficient attention was not directed to the quantity and quality of the food, the results were quite definite. In some of the cases there was an immediate rise in the uric acid output; in others the excretion rose during the second or third day of a severe attack up to 2 to 5 decigrammes and more above the former values, and often remained abnormally high for several days. Similar observations were noted, as has been already mentioned, by Vogel, Ebstein and Sprague, Badt, Watson, and others (37). This increased excretion is accepted as a permanent and regular fact in the works of Minkowski and of Wiener.[1]

The increase which is noted at the time of the gouty attack, and which is especially conclusive, is observed even when the patient is on a purin-free diet.

Example from Brugsch's Work (7): *Purin-free Diet* (*Case II.*).

	Uric Acid (Gm.).
Acute attack	0·708 0·675
Four days' interval	0·376 (average)
Acute attack	0·618 (one day)
Later days of the attack	0·375 (average of eight days)
Slight attack	0·585 (average of two days)

[1] Definite proportional relations between the extent of the uric acid shower and the severity of the attack were not recognisable, especially in the cases of Magnus-Levy and of Brugsch.

One must regard this paroxysmal uric acid shower as typical to a certain extent, although exceptions are known (one observation of His, two others of Zagari (9) and of Vogt (7)].

Often a slight decrease in the uric acid excretion, which lasts for one to two days, precedes the increase. This first period of depression, as it has been called, is, however, not a regular phenomenon. It is completely lacking at times, and does not alone suffice to explain the uric acid shower which immediately follows it.

Much more regular is the marked decrease of the uric acid excretion which follows the increase, and which is designated the second period of depression. This appears even during the height of the gouty swelling, or immediately after its subsidence. At this time the excretion of exogenous purin bodies is markedly affected. Brugsch's calculations from the tables of Kaufmann and Mohr (7) illustrate this point :

In their observation No. 41 such a patient received about 300 grammes of calves' thymus on each of four days. A total increase of about 1·2 grammes in the purin nitrogen of the urine was to be expected. There were actually excreted only 0·471 gramme of this, and that, too, only after some delay.

In their investigation No. 42 an increased excretion of 0·90 gramme nitrogen was to be expected (300 grammes of calves' thymus on each of three days). However, only 0·187 gramme appeared in the urine.

In the periods which were more remote from the acute attacks, the excretion of the purin substances which were administered was much more favourable (observations Nos. 39 and 40).

As has been already mentioned, the diminution of uric acid which often immediately precedes the attack is not sufficient to compensate for the excess which appears during the attack. One must assume a retention of uric acid which has extended over a long period of time. Nothing is known for certain regarding this, although there is much which points to such a conclusion.

When Pfeiffer first observed the paroxysmal uric acid shower, he considered it as a long-continued retention followed by a sudden overloading, and assumed that, for some reason or other, the alkalinity of the blood and of the tissue juices was increased, and that the uric acid consequently was dissolved in the gouty deposits. This led to the further view that the dissolved uric acid causes, on the one hand, gouty inflammation, and on the other the uric acid shower in the urine, the preceding uric acid retention being the cause of the paroxysmal uric acid shower. Pfeiffer has now probably discarded the untenable idea that the alkalinity relations of the blood were of importance in this connection. An explanation of the irregular phenomena of gout by changes in the alkalinity of the blood and lymph is not now admissible. It is more practical to think of other chemical processes which exert an influence on the combination and solution of uric acid. I will refer to this point later.

A further question is whether the increase of the uric acid excretion has the same origin as that observed in other non-gouty acute febrile conditions—that is to say, whether it is the result of toxogenic decom-

position of protein in which the nuclein substances of the body are at the same time concerned.

I must raise this question, although I do not believe that it can be answered in the affirmative. According to the figures of Pfeiffer, His, and Magnus-Levy, the uric acid increase in gouty attacks is still greater than is observed in the correspondingly severe febrile conditions of different origin. It is to be hoped that later more exact metabolic investigations which have to do with the excretion of nitrogen and of P_2O_5, as well as of uric acid, will disclose what part of the uric acid increase during the gouty attack must be referred to toxogenic tissue decomposition, and what part to the specific gouty process.

Meanwhile all the points which have been settled seem to indicate that uric acid retention occurs in the gouty subject, and that this retention may be markedly interrupted by increased uric acid excretion during the acute attack, and less markedly influenced in the attack-free intervals.

8. Uric Acid in the Blood.

(*a*) *The Uric Acid Contents of the Blood.*

If we trace the metabolic processes a step further back we find, in the first place, an increase of uric acid in the blood. This fact was discovered by Garrod, and at one time appeared to clear up the mystery of gout.

The few known facts may be detailed as follows :

1. Only traces of uric acid can be detected in normal blood.

2. In conditions which are accompanied by marked nuclein decomposition—for instance, in pneumonia and leuchæmia—uric acid can be demonstrated in the blood. To this group belong also the ingestion of excess amounts of thymus [Weintraud (50)], of meat-extract [Strauss (51)], and of nuclein [Bloch (51B)], as well as of an excessive meat diet [Schur (51A)]. The explanation of the condition is very evident. The increased amount of uric acid which arises from the decomposing tissues or from the food is taken up by the blood, and the kidneys can hardly keep pace with the mass brought to them for excretion. The values are often higher than are ever observed in gout, but uric acid is not deposited in the tissues, not even in the chronic uricacidæmia which accompanies leuchæmia.

3. In nephritis the uric acid of the blood is increased [Garrod, von Jaksch]. In this case it is not an increased supply, but rather a retention arising from the renal insufficiency, which is the cause of the condition. Since the diseased kidney, especially the contracted kidney of chronic interstitial nephritis, excretes large amounts of uric acid, and markedly increases this excretion if proper substances are administered, it has been assumed that the uric acid of the blood must first reach a higher level before the diseased kidney is capable of excreting it [Magnus-Levy (3)].

Even if the overloading of the blood with uric acid which is observed

in nephritis continues for months and years, it does not, as a rule, lead to gout. I will discuss this point again later.

4. In gout the blood contains increased quantities of uric acid. It is Garrod's immortal service to have recognised this fact, in spite of imperfect methods of detection (so-called thread test). When, however, he concluded from the results of his reactions that uric acid accumulates in the blood before the acute attack, and is considerably diminished after the paroxysm, he went rather too far. In five quantitative—but not trustworthy—estimations, Garrod (52) found 25, 30, 50, 11, 175 milligrammes of uric acid in 1,000 c.c. of blood. Isolated blood examinations by Salomon (53), and four such determinations by G. Klemperer (54), showed a similar uric acid increase (44, 67, 88, 91 milligrammes of uric acid in 1,000 c.c. of blood). Yet these figures do not permit any definite inference as to the relations of uric acid during the attack and in the attack-free periods. We must thank Magnus-Levy (3) for the first comparative, and at the same time comprehensive, investigations along these lines (thirty-four researches on seventeen patients). In 1,000 c.c. of blood he found 30 to 80 milligrammes of uric acid. The average values were 50 to 70 milligrammes of uric acid in 1 litre of blood, or, calculated in terms of total volume of blood, 250 to 350 milligrammes. Valid variations in the uric acid content—that is, an increase preceding and during the attack—as Garrod, Bence-Jones, Charcot, Ranke, Duckworth (55) taught, and as Salomon also thought he had found, were not observed by Magnus-Levy.

It is not necessary in this place to enter into a discussion regarding the results which Haig (56) wished to add to the above, for his method of determining the uric acid in the blood is, as Luff (57) has already emphasized, absolutely useless.

These analyses of the blood contents do not at all suffice to explain the excretion, for the blood-serum is able to dissolve much more uric acid than it is called upon to do, either in health or in disease [Klemperer (54)]. This work of Klemperer has been minimized by the suggestion that the uric acid may, perhaps, be destroyed and not actually dissolved. Some observations which I carried out immediately after the appearance of Klemperer's investigations appeared to indicate that solution and destruction of uric acid may go hand in hand.

Klemperer added to the serum a weighed amount of uric acid, digested the mixture for four hours with frequent shaking, and weighed the residual uric acid. I supplemented this by a direct uric acid estimation of the blood so treated : 160 c.c. of serum, obtained at the beginning of a severe attack of gout, were divided into two equal parts. The first half contained 6·9 milligrammes of uric acid (the equivalent of 86·2 milligrammes in 1 litre). The other half was treated in the manner prescribed by Klemperer with 302 milligrammes of chemically pure uric acid. There remained undissolved 150 milligrammes, while from the serum was obtained 41 milligrammes. Thus 34 milligrammes of uric acid were dissolved by the serum, which now contained 512·5 milligrammes in a litre. There remained 268 milligrammes of uric acid to be accounted for.

In a later publication Klemperer (58) stated that uric acid was de-

stroyed during the mixing with the total volume of blood, and that oxalic acid and urea were formed. On the other hand, Trenkner found that the serum of healthy and diseased subjects does not dissolve uric acid. In fact, he found that serum loses its uric acid dissolving power after incubation. Ritter (58A) had reported earlier that already dissolved uric acid could be again separated from the serum. Trenkner did not investigate any blood-sera which were obtained from gouty patients. It is perhaps an accident, perhaps an important finding, that some serum I obtained during an acute attack showed a strong uric acid dissolving, and at the same time a marked uric acid destroying, power.

Taylor (58B) estimated the solubility of uric acid in the blood-serum of oxen, and found it to be 1 : 1,000—that is, thirty-five to forty times greater than in distilled water. The alkalinity is not responsible for this, because the serum was intentionally acidified, and, moreover, the normal blood is generally neutral ; free cations are not present therein [Fränkel, Farkas, Höber (58C)]. The taking up of uric acid by the blood-serum does not change its electric conductivity. From this fact Taylor justly concludes that the uric acid does not exist in simple solution, but in some firm organic combination.

This exhausts the facts which we know regarding the uric acid of the blood. Of the true nature of the combination in which uric acid circulates we are quite ignorant.

(*b*) *The Uric Acid Content of the Blood in Gout and Nephritis.*

The diminution of uric acid in the urine of the gouty—which the older methods unduly accentuated—the overloading of the blood with uric acid in gout and in nephritis, and the frequent coincidence of both diseases, have induced a number of investigators to assume that in gout the excretory power of the kidney as regards uric acid is interfered with, even in those cases in which no clinical signs point to nephritis. The primary cause of the uric acid retention in gout lies, according to Garrod, in the kidney. Later authors went further than Garrod, and spoke not only of functional disturbances of the kidney, but also of anatomical changes (especially interstitial nephritis) as conditions preliminary to gout. Recently Levison and Luff, and, with certain reservations, also Strauss (58A), have advocated the same view. Levison and Luff showed, in a very large series of post-mortems in Denmark and in England, that in cases of interstitial nephritis, uric acid deposits in the articular cartilages are very frequently found, although the condition was not suspected during life. Stripped of all unnecessary detail, this means that the retention of uric acid in the blood and the remaining phenomena of gout are the results of a primary disease of the kidney. In certain cases both nephritis and gout are amenable to clinical diagnosis. In other cases nephritis, and in still others the uric acid diathesis, remain for a long time, perhaps even up to the end of life, clinically free from symptoms and unrecognised. No one, I am sure, will have the courage to infer from the Garrod-Levison theory that gout has not a special

place in nosology, and is only an associated condition, or, at most, a complication of nephritis.

The figures of Levison and Luff show, in the first place, that nephritis and gout occur in the same individual more frequently than was formerly assumed. They recall to us the facts that harmful influences, especially alcoholism and saturnism, and also heredity, play an acknowledged part in the etiology of both diseases. It is not possible to show the dependence of gout on interstitial nephritis by statistics. So much the less likely is this as these statistical data are not absolutely suited to every series of cases observed. Minkowski (1) has sought in vain for uric acid deposits in the cadavers of typical cases of interstitial nephritis. It is to be noted, however, that his material was not large. Weigert, at my instigation, for many years always opened the metatarso-phalangeal joint of nephritics, but very exceptionally found deposits of urates.

I lay more weight upon the negative evidence than upon the positive results of Levison and others, inasmuch as these latter may perhaps be influenced by local conditions. It appears that continuous overloading of the blood with uric acid (nephritis) does not necessarily lead to gout, and, moreover, that this overloading is not followed by uric acid deposition without the accession of another, still unknown, specific gouty factor.

(*c*) *Causes of Uricæmia.*

When there is an increased formation of uric acid, it is not difficult to account for the uricæmia. In gout, however, except, perhaps, in the acute attack, there is no reason to assume an overproduction of uric acid. As a rule, nuclein-poor food is prescribed for the gouty individual, and —again disregarding short transitory periods—no signs are obtained of an increased decomposition of nuclein beyond, perhaps, an increased phosphoric acid excretion.

It lies much nearer to hand to assume a deterioration of the excretory conditions. This assumption cannot, at any rate, be rejected on such good grounds as the teaching of an overproduction of uric acid. In this connection two hypotheses present themselves.

1. With the appearance of the gouty condition the kidney cells are so influenced by unknown toxic substances that they are able to withdraw uric acid from the blood only when the solution tension of this acid reaches a higher limit than is the case in nephritis [Magnus-Levy (3), Minkowski (59)].

We must assume a renal insufficiency of a peculiar specific type, for which no anatomical basis is known. Such functional disturbances without anatomical changes are familiar to us to-day. I recall in this connection what was said regarding the function of the pancreas in diabetes. It is not practicable to distort the facts and to diagnose a latent nephritis as the cause of the gouty processes, and especially of the uric acid retention, in those cases in which no other clinical sign points to a nephritis. If a renal insufficiency as regards uric acid is actually the cause of the overloading of the blood and tissues of the gouty with

uric acid, then it must be of a different type to that which obtains in ordinary nephritis. For, aside from the most extreme cases of nephritis, the uric acid elimination of the nephritic patient is incomparably better than that of the gouty subject.

The baneful influence of the specific gouty process might in time extend its line of attack, and thus lead to the clinical picture of the gouty kidney (anatomically a granular kidney). Gout produces nephritis according to this view, but nephritis does not produce gout. Nephritis, once established —no matter whether in dependence on gouty processes or as an independent complication—can then further assist in the overloading of the blood with uric acid. I call to mind the conditions in diabetes mellitus. This frequently leads to albuminuria, and pure nephritis occurs as one of its complications. The nephritis may, in its turn, aid in increasing the hyperglycæmia.

2. Uric acid circulates in gouty blood in a combination which makes it less capable of being excreted in the urine. Pfeiffer (46) was the first to express this view, but he made the mistake of laying altogether too much stress on the alkalinity of the blood. On the basis of other confirmatory evidence, Minkowski (60) arrived at the same conclusion. Simultaneously with Goto (61), Minkowski showed that uric acid can enter into combination with other cleavage products of nucleinic acid, especially with thymin or nucleotin-phosphoric acid. This finding has been confirmed by His (62). Thus combined, uric acid is not precipitable by acids, and escapes detection by the ordinary methods of examination, unless the compound is previously broken up by boiling with dilute sulphuric acid.

According to Minkowski, under normal conditions uric acid probably circulates in this form in the blood, and as such is easily dealt with by the renal cells. It is extremely doubtful, however, whether it is really nucleinic acid and its derivatives which are responsible for the transportation of the uric acid through the blood. The addition of the sodium salt of α-thymo-nucleinic acid to the intravenously injected uric acid does not, in animal experiments, facilitate the uric acid excretion [Schittenhelm and Bendix (63)]. Above all, no one has succeeded in demonstrating the presence of a compound such as the nucleotinic-acid-uric acid combination in the blood.

In spite of this, the existence in the blood of some sort of an organic uric acid compound, which is of importance for the circulation of uric acid, seems very plausible. The uric acid is completely precipitated from the acidified urine by the use of the centrifuge [W. His]. The uric acid is, then, actually present as uric acid. In the case of the blood-serum it is quite another matter. From 200 c.c. of blood-serum, obtained from an animal fed with excess of nuclein-containing food, 8 milligrammes of uric acid were found by analysis, while after centrifuging only 4·3 milligrammes were recovered [Bloch (51B)]. Hence a part of the uric acid is more firmly bound, but not in the form of a salt. The why and wherefore of this is, however, still completely obscure. To become master of this question is certainly one of the most important problems in the investigations of gout.

9. The Uric Acid Deposits.

The gouty deposits, which are at one time slight, at another extensive, and are observed in the cartilages, articular sheaths, tendons, muscles, skin, etc., impress one as being legitimate offspring of the gouty diathesis. These deposits are pathognomonic. When they are present, the diagnosis of gout is certain, aside, perhaps, from a few exceptions. This statement cannot, however, be reversed, for there are typical cases of gout in which uric acid deposits are lacking, or are present only in traces. The early stages of the disease may be cited in this respect. The patient is often a victim of gout for a long time before the deposits appear and bring the diagnosis within the sphere of the senses. The gouty inflammatory processes in the joints, tendons, and muscles may be considered as fundamentally equivalent to the tophi. One is an acute, the other a chronic, process. The most important facts in this connection are the following :

1. The deposits consist essentially of sodium biurate [Wollaston, 1797]. The analysis of two tophi gave the following composition of the dry substance [Ebstein and Sprague (64)].

	I.	II.
	Gm.	Gm.
Uric acid	59·7	61·27
Tissues	27·88	26·45
Na_2O	9·3	12·28
Ka_2O	2·95	—
CaO	0·17	—
MgO, Fe, P_2O_5, S	Traces	—

The deposits have certain favourite sites, among which the joints, which are affected by the inflammatory processes of gout, are especially conspicuous. Yet they may occur in almost any part of the body. The nervous system alone seems to possess a certain, if not an absolute, immunity. Regarding the frequency of their appearance in the various parts of the body, text-books of pathology and of pathologic anatomy may be referred to.

The sluggish circulation within the cartilaginous tissues has been considered the cause of the predilection of such tissues. Important and interesting investigations regarding the chemical relations between uric acid and cartilaginous material have been recently published [Almagia, Pfeiffer (64A)]. Cartilage possesses an especially high physical and chemical absorptive power for urates. It is in a position to attract urates, which are introduced into the circulation. If it is true, as has been frequently emphasized in this chapter, that retention of uric acid is present in gout, then the discoveries of Almagia have advanced us much nearer the recognition of the pathogenesis of uric acid deposits and of their localization.

2. Uric acid is toxic, and induces inflammatory processes in the surrounding tissues. It does this, however, only if it is in a strong concentrated solution. Solid needles of sodium biurate do not stimulate the adjacent

tissues, but rather act only as foreign bodies [Ebstein, von Loghem (65)]. Fever appears as a general reaction [Soetbeer and Ibrahim (8)]. In confirmation of Garrod's old teaching, Freudweiler and His (66) observed the appearance of inflammatory foci after injection of mono-sodium urate. The course and resolution of these foci showed the greatest similarity to the acute inflammatory foci of gout. They assumed on good grounds that the urate must be partly brought into solution before it can exert its toxic action. In this they approximate the hypothesis of Ebstein, the first part of which runs as follows : The dissolved uric acid, which circulates in the tissue juices, leads, if local stasis be present, to inflammation, and later to necrosis. With the toxic properties of uric acid the following facts are in accord. Frequently the local processes, which are dependent on the action of uric acid, proceed with violent acute inflammation and marked febrile reaction, while at other times these processes develop very slowly without any striking phenomena, and with sluggish reaction of the tissues. Other poisons act similarly. The kind of tissue, the condition of the circulation, concentration of the poison, continuance of its action, tolerance of the system, and production of antitoxines determine the differences. This theory has, it is true, one point of attack. The chemical demonstration of increased amounts of uric acid in the fresh gouty foci of inflammation is lacking. It is not sufficient that uric acid be found in exceedingly dilute concentration in the exudate of gouty joints [Magnus-Levy (3)], for this acid is present also in different exudates and transudates which occur in patients in whom there is not the slightest suspicion of arthritis urica [Naunyn, Pickardt (67)]. The possibility remains that another specific toxic substance is the real poison [von Noorden, Likhatscheff (68)]. It may be that uric acid is produced in the diseased tissues (von Noorden), and cannot, as a result of the chemical peculiarities of the process, be held in solution, and thus be carried away; or it may be, owing to the chemical peculiarities of the process, that the uric acid is precipitated in the diseased tissues from the circulating fluids [Klemperer, Strauss, opposed by Freudweiler (69)]. In view of the certain relation of uric acid to the local and general phenomena of gout, in view of the demonstration of uric acid in the later stages of the attack, and in view of its undoubted properties of producing inflammation and fever, it seems almost unnecessary that a second irritant should be deemed the causative factor in the inflammatory process. Yet, notwithstanding this, we may regard it only as a possibility—at most as a probability—that uric acid is the true all-sufficient cause of the acute and chronic, local, inflammatory, and trophic changes of gout.

3. All attempts to explain the deposition of crystals by changes in the alkalinity of the blood and tissue fluids have failed. Just as uncertain are the changes in molecular concentration. The solution of the solid needles is also not a result of changes in alkalinity, but is brought about by phagocytosis and by the fermentative processes which are associated with it.

When I reject, at this time, the relations between the anomalies of tissue and blood alkalinity and the deposits of urates, this refers

primarily, as I expressly state, only to gout in man. In this connection there is not the slightest evidence in favour of the presence of such relations. It should not be disputed that, in cases of artificial deposits of urates (intramuscular injection of uric acid, etc.), the introduction of acids and of alkalis into the body plays an important part in the fate of the injected urates [von Loghem (69A)]. Uric acid, injected into dogs, vanishes completely in the tissues. However, deposits of urates are obtained in dogs at the site of the injection if large doses of sodium bicarbonate are given to them. The conversion is brought about, according to von Loghem, by an exudation which contains leucocytes. The case is different with rabbits. Urates are formed from the injected uric acid, simultaneous administration of hydrochloric acid retarding or preventing this process. No evidence has as yet been obtained which will explain the appearance and disappearance of the spontaneous gouty deposits in man.

What is the cause of the absolutely different behaviour of uric acid in gout as contrasted with other diseases ? To bring into the foreground the alkalinity of the fluids and tissues seemed to the old school the easiest solution. Garrod, Cantani and Pfeiffer regarded the lessening of the general alkalinity of the blood, while Ebstein considered rather the local variations of the tissue alkalinity. The theory of Pfeiffer (46) is the most worthy of mention and the best conceived. Lessening of the alkalinity of the blood should bring about a deposition of urates. If, then, the alkalinity of the blood again increases at certain times, uric acid will be dissolved at the point of its deposition. The dissolved urates cause, on the one hand, local inflammation (the acute attack of gout), and, on the other, the uric acid shower in the urine.

I believe that I was the first to express myself as emphatically opposed to the idea of over-rating the alkalinity relations of the blood (70).

At that time only meagre data were at hand regarding the reaction of the blood and tissues in gout. Reports had been previously published showing somewhat high values for the alkalinity of the blood, both in the acute attack [Pfeiffer (71)] and in chronic gout [Jeffries, Drouin (72)]. The later investigations of Klemperer, Magnus-Levy, Strauss, Watson, Luff, and Löwy (73) have shown, as a rule, normal relations, with here and there a slight increase, but never any decrease, in the alkalinity of the blood. Also no remarkable deviations from the normal relations were recognised in the comparative estimations during the attack and in the attack-free periods [Magnus-Levy (3)]. In the only disease—namely, severe diabetes mellitus—which is associated with diminished alkalinity of the blood, and runs a very chronic course, deposits of urates do not appear, although in diabetes the conditions are present which, according to the old theory, favour the deposition of uric acid (the more abundant meat diet and the frequently complicating renal disease). All the hypotheses which have been advanced regarding the changing relations between the alkalinity of the blood and gouty deposits are unsupported by facts.

The same thing must be said regarding the relations of local changes

in alkalinity to uric acid precipitation. These relations are a large factor in Ebstein's theory. Mordhorst (74) adds to his advocacy of alkaline substances a remark which I cannot allow to go unchallenged, because it gives, apparently, expression to a widespread view. He says: "That the tissue fluids in the region of the gouty deposits must be acid follows from the fact that uric acid and its acid compounds are precipitated only in acid fluids." Now, as a matter of fact, the needles in the gouty deposit consist of acid sodium urate, whose solubility decreases, as has been since determined, with increasing alkalinity of the medium. Moreover, the statement is absolutely incorrect that the reaction is acid in the region of these deposits. I have in several cases examined the deposit, which is easily expressed from freshly-opened, rather early tophi, and have found it distinctly alkaline to litmus and lacmoid. The material obtained in this way was chiefly composed of acid urate crystals [von Noorden (75)]. The fact has also been frequently confirmed that these crystalline acid compounds are held in an alkaline medium. In another place I advanced the idea that the urate deposits disappear, or, as frequently happens, are reduced in amount, owing, not to the changed alkalinity of the fluids, but rather to the avidity of certain cells [von Noorden (76)]. It has been experimentally confirmed by Freudweiler (66) and Rindfleisch (77) that the solution of the deposited urates is a process of phagocytosis. Only the free uric acid, which, however, does not come into consideration in gouty deposits, is directly dissolved by the fluids of the tissues and of exudations [von Loghem (77A)]. This agrees very well with the observation that blood-serum also exerts a dissolving or destroying power upon free uric acid.

In addition to the no longer tenable theory which associates the deposition of urates and, further, the whole origin of the gouty foci, with variations in alkalinity, one must mention the theory advocated by Roberts (78), Mendelsohn (79), and recently by Strauss (51). According to this theory, the urates are deposited in the diseased tissues owing to abnormally high content of sodium chloride or of metabolic refuse of different kinds. It is certainly true that the solubility of the urates, and especially of uric acid, depends, to a great extent, on the molecular concentration of the solvent [His and Paul, Klemperer, von Loghem, and others (80)], but this fact does not warrant far-reaching conclusions. Even if those molecular concentrations were found in gouty foci, which, *in vitro*, sort out urates from watery solutions (which is not the case), there would arise a marked and, as regards its extent, an absolutely unknown counterpoise of the molecular concentration with the colloidal properties of the tissue fluids.

Recently Kionka (80A) published, in collaboration with Frey, certain broadly-planned researches, in which he attributes to amido-acetic acid an essential rôle in the origin of uric acid deposits. It would lead us too far to discuss this theory, especially as the bases of Kionka's hypothesis are not too well grounded. He referred, among other things, to the detection of glycocoll in gouty urine [Ignatowski (80A)]. This finding has, however, lost its meaning [Lipstein, Fossnar (80A)]. Chemical

objections have also been raised against this phase of the new theory [Abderhalden and Schittenhelm (80A)]. Regarding Kionka's theory, reference must be made to his original articles.

While it is clearly enough established that the disappearance of the uric acid deposits is due to processes of phagocytosis, we know, unfortunately, nothing certain regarding the theoretically most important period of the disease—that is, regarding the incipiency of the local phenomena of gout. Ebstein assumes, as is well known, that uric acid is present in the first place in the dissolved state, in which condition it causes inflammation and necrosis. The sodium biurate needles are later deposited in the necrotic tissues. No deposition of urates without preceding necrosis is the tenor of the theory. In spite of the efforts of Schreiber and Zaudy (81) to the contrary, this is refuted by Riehl, Aschoff, Freudweiler, recently,[1] also, by Rosenbach and Litten (82), who found urate needles in absolutely healthy tissues—as, for instance, in the region of tophi and in the kidneys. If Ebstein failed to find them, his methods of preparation were at fault, in that the urates passed into solution and thus escaped detection.

Moreover, it has recently become doubtful whether necrosis in the gouty tophi plays, in general, such an important rôle as one must assume, according to Ebstein. It appears, rather, to be more a question of secondary pressure atrophy brought about by the concretions than one of tissue death [Minkowski, Krause (83)]. Necrosis, although doubtless present [Rosenbach], plays a subordinate part.

Clinical facts also speak against Ebstein's assumption that overloading with uric acid is always the primary phase, while deposition of urates is secondary. We often see tophi slowly increase in size without any reaction. They extend their branches, as Riehl and Aschoff showed, into absolutely healthy tissue. Delay is occasioned at the boundaries of the foci. Either absorption or growth gets the upper hand, when an acute or subacute inflammation appears, often without any outside cause, often following a bruise or overexertion. Frequently only one focus is involved; frequently many, either simultaneously or successively, are affected. After the inflammation subsides the tophi are smaller, or have disappeared. If an enlargement of the focus remains, it is to be attributed rather to the diffuse swelling of the surrounding tissue than to the tophus itself. The tophus later grows again very slowly. All of this occurs in places so favourably located that our eyes can easily detect the stages in the process. It is true, or at least apparently so, that the course of events may be of a different sort. In a previously healthy site the local inflammation may be the first symptom of the disease. After this subsides the tophus develops. These cases, which are not at all rare, were used as proofs of Ebstein's theory. He cannot, however, overcome the objection that previously there had occurred in that place a diffuse reactionless infiltration with urates, which was just as

[1] Schreiber and Zaudy supposed that the crystals which were found at the periphery of the gouty focus, etc., should be considered as agonal or as post-mortem formations. Litten and Rosenbach proved that giant cells and lymphocytes (urophages) were present in the region of the crystals.

inaccessible to observation as are the deposits of urates which are doubtless present in the metatarso-phalangeal joint during the attack-free intervals of the disease. After subsidence of the inflammation the deposit increases, being favoured by the tissue changes which the former condition has left.

Owing to the complete lack of knowledge regarding the anatomical changes which are present in the early stages of the acute paroxysm, the question cannot, naturally, be decided with certainty. It is, however, probable that deposition of urates must have taken place preceding the attack, in which case one will willingly make the concession to Ebstein that the conditions would be especially favourable for their excretion, providing a marked local inflammation was immediately associated with the deposition. That this is not always the case has been mentioned.

If we survey what has been said, we find that the reasons for the deposition of urates are absolutely unknown, and that it is as yet undecided whether the uric acid in the foci is autochthonous in origin, or is derived from the blood. The latter idea is probable, in view of the fact that the deposits are frequently very large, and tend to rapidly increase in size. An associated autochthonous formation is, however, not excluded.

The urate needles may be deposited in a tissue which, from the microscopical standpoint, is anatomically quite normal. Whether the tissue is at the same time chemically sound must remain doubtful.

The absorption of the urates is brought about by phagocytosis. Whether, besides this, other chemico-fermentative processes play a rôle is uncertain. In so far as foci of gouty disease are concerned, nothing is known regarding the action of changes in alkalinity.

It is not a far cry to conclude with Pfeiffer that if, for any reason whatsoever, a sudden solution of the deposited urates occurs, there arises, owing to the toxic action of this (primarily intracellular) solution, a local paroxysm, and, later on, a febrile reaction of the entire organism. It is uncertain whether this is a true causal relationship, or whether the absorption of the urates, local inflammation, and general reaction, are not common results of a chemical process peculiar to gout.

A further question is whether the uric acid which passes into solution is completely destroyed, or whether it shares in the uric acid shower in the urine.

It is evident, therefore, that we know little regarding the fate of the gouty foci. Many questions still remain to be settled.

10. Uric Acid in the Sweat.

The perspiration of the gouty subject has often been examined for uric acid. Garrod, who (85) cites and criticises the older, alleged positive, results of Swediaur, Golding-Bird, and C. Petit, asserted that he had once found traces of this substance. As a rule the perspiration is free from uric acid. The same finding was reported by Lehmann, Bouchard, Martini and Ubaldini (86), while Kühne (87) detected its presence, and

Tichborne (88) once found marked traces of it in the perspiration induced by the Turkish bath. I, personally, have only failures to record. Eight cases were investigated, in which the perspiration was stimulated by hot-air baths or by pilocarpine. The same negative result was given by the experiments of Magnus-Levy (3). It may be remarked in passing that the perspiration of the gouty patients showed on analyses 0·03 to 0·04 per cent. of nitrogen.

In marked contrast to the negative findings in gout stand a few positive results in nephritis (see Vol. II.). It is possible that in those cases of gout in which other authors found uric acid in the perspiration, the kidneys were sympathetically affected to a marked degree.

At any rate, it is not a function of the production of perspiration in the gouty to really compensate in certain respects for the deficient excretion of urates in the urine.

11. Excretion of Uric Acid by the Digestive Organs.

Boucheron (89) claimed to have found uric acid in the saliva of gouty subjects. In two patients from whom I obtained by pilocarpine injection 320 and 530 c.c. of saliva I searched for uric acid with absolutely negative results.

Nothing reliable is known regarding the excretion of uric acid by the mucous membrane of the stomach or intestines. Hayem (90) is the only one who asserts that he once found deposits of urates on the intestinal villi; no chemical proof supported this statement. When Ebstein, and recently His, assert that the toxic properties of uric acid play a definite etiological part in the digestive disturbances of the gouty, one may indeed regard this as a valuable incentive to further study, although at present it is purely hypothetical (*cf.* Purin Bodies).

V.—INFLUENCE OF GOUT ON THE BLOOD.

1. Alkalinity. Uric Acid.

Regarding uric acid in the blood and the alkalinity of the blood, see pp. 667, 674.

2. Concentration.

Garrod (92) frequently estimated the specific gravity of the blood. He reports the average in chronic cases as 1027 to 1028, scarcely ever below 1025. The same figures obtained for the period of the acute attack—that is to say, they approximate normal. Magnus-Levy (91), Grawitz and von Limbeck (93), found similar results. When lower values occur, they are usually due to inanition or an associated albuminuria.

3. Morphology of the Blood.

Little information is available as to the content of the blood in red and white corpuscles. Deviations from the normal have not been observed. A few cases which Grawitz and von Limbeck (93) investigated showed normal relations. Ten Cate (94) records remarkable results. In a severe case of gout there was no leucocytosis after feeding with thymus. I have at my disposal a similar observation. A gouty subject, during a period of recurrent attacks, was fed for several days on a purin-free diet. At 12 noon 8,500 leucocytes were found in 1 c.c. of blood. At 1 p.m. he received 350 grammes of thymus. At 4 p.m. the leucocytes numbered 8,800. As a control, a nephritic patient was examined under exactly the same conditions. The corresponding leucocyte counts were: midday, 7,860; three hours after the meal of thymus, 9,900. This agrees with the increase which Milroy and Malcolm (95) have observed in healthy subjects a few hours after taking nucleinic acid.

Neusser (96) writes that in uric acid diathesis leucocytes are present in the blood whose nuclei are surrounded by basophile granules (perinuclear basophiles). Kolisch reports the same findings. This phenomenon, which might have been of great importance in the diagnosis of gout, is found, according to T. B. Futcher (97), to exist in many other diseases. Ehrlich (98) doubts the accuracy of the observations, and regards the basophile granules described by Neusser as artifacts which were caused by precipitation of pigment. Walker Hall observed an increase in the basophile cells of the blood after long-continued injections of hypoxanthin into rabbits. Chalmers Watson (7) describes large degenerate white cells as occurring in one of his cases of gout. I have no personal observations on this subject at my command.

4. Molecular Concentration.

A few figures of Waldvogel and Strauss (99) are available as to the molecular concentration of the blood. These investigators observed one patient each, and found that the lowering of the freezing-point during the attack was remarkably high (Waldvogel $-0{\cdot}82°$, Strauss $-0{\cdot}76°$). Waldvogel's patient had a diseased kidney, while the patient of Strauss was apparently healthy as regards his kidneys. In two other patients Strauss found, during the attack-free periods, $-0{\cdot}56°$ and $-0{\cdot}53°$. Likewise, in Waldvogel's case, the molecular concentration was lower after the attack (freezing-point $-0{\cdot}56°$). An interpretation of these results cannot as yet be hazarded. According to Strauss, the accumulation of nitrogenous products of metabolism appears to be concerned in this phenomenon. He found 60 to 80 milligrammes of nitrogen in 100 c.c. of serum from which the albumin had been removed.

Also in another case of gout which was complicated with pulmonary tuberculosis Strauss (99A) found 79 milligrammes nitrogen in the filtrate.

Lowering of the freezing-point was 0·59°. The normal filtrate nitrogen is about 35 milligrammes.

These high values recall the fact that Garrod (100) and Budd also found somewhat increased amounts of urea in the blood. The most probable explanation is, I believe, that in all these cases an insufficiency of the kidney exists as a complication.

5. Oxalic Acid.

Garrod observed the presence of oxalic acid in the blood, especially at the height of the paroxysm. On applying the thread test, its calcium salt separated from the serum as a crystalline deposit. He referred the oxalic acid to the decomposition of uric acid. I am unable to find any later investigations and comparative analyses of healthy and of gouty blood in cases where attention was paid to the diet.

VI.—THE URINE IN GOUT.

Excretion of nitrogen (see Protein Decomposition, p. 647).
Uric acid and alloxur bases (see p. 655).

1. Quantity.

At the beginning of the attack the amount of urine is usually small, the specific gravity is high, and a sediment falls when the urine cools. The appearances of gouty urine resemble those of ordinary febrile urine. Frequently enough patients show febrile reactions during the attack. After a few days—usually before the disappearance of pain and of the local inflammation—the urine is again abundant and less concentrated.

In the attack-free intervals of regular gout striking changes in the amount and in the specific gravity of the urine are not common. In other cases the urine is excreted more abundantly and less concentrated. This is very often the case in the chronic atypical form. In case such changes do appear, the possibility exists that a contracted kidney has developed along with the gout. Yet one must take into consideration the copious fluid intake (mineral waters, etc.) of many gouty subjects.

2. The Various Nitrogenous Substances.

Further investigations on the several nitrogenous substances of the urine are wanted, as a pathologic type of protein decomposition in this disease has already been discussed. In this connection we must consider urea, ammonia, and monamido acids. The alloxur bodies must be left out of this consideration, inasmuch as they arise from special sources. Sufficient reference has already been made to their relations in this disease.

(*a*) *Urea.*

Camerer (101) found in three gouty subjects 89·9 to 91·7 per cent. of the total nitrogen as urea; Vogel, by the use of the phospho-tungstic acid method, obtained values of 82 and 92 per cent. in ten out of fourteen estimations on three patients. When the figures approach, and even pass, the lower limits (in four determinations the values were between 71 and 79 per cent.), this is due to a marked diminution of the urea itself or of the total nitrogen rather than to an increase of the residual nitrogen. The phenomenon corresponds to the previously described general retention of nitrogen.

We have to thank Boedtker (102) for numerous estimations of urea by the Mörner method. In typical cases, the values lie in the attack-free intervals, between 85·3 and 94·1 per cent. (91·1 per cent. as the average of twelve determinations). During the acute attack the figures vary between 83·94 and 93·29 per cent. (90 per cent. as the average of fourteen estimations). In chronic cases, with persisting gouty disease of the joints, 82·11 and 94·13 per cent. were observed (87·97 per cent. as the average of ten analyses). These figures do not permit of accurate conclusions. It is possible, but not exactly probable, that a further study of these relations may furnish better explanations.

(*b*) *Monamino Acids.*

Ignatowsky (103) found—by the β-naphthalin-sulphochloride method—an increase in the amino-acid output in gout. Lipstein observed 1·06 to 1·58 grammes daily, figures which were considerably higher than those of Ignatowsky, but which were entirely within the normal limits (1·32 to 2·80 grammes) [Embden and Reese]. Fossnar (104), who likewise used the improved method in continuance of the investigations of Ignatowsky, comes also to the conclusion that nothing in the behaviour of the amino-acid excretion can be regarded as characteristic for arthritis urica [see also (104)].

(*c*) *Ammonia.*

The ammonia determinations are of special interest, because the height of the ammonia excretion is to be regarded as an index of acidity, and because the chemical reaction of the blood has from the beginning played a great rôle in the theories of gout. The investigations of Camerer (106), Vogel (5), and Magnus-Levy (3) all agree in the finding of normal values for the absolute amount of the ammonia excretion, and for its relation to total nitrogen. This finding, which is not without importance in the theory of gout, holds for all stages of the disease. Yet we cannot but wonder if occasionally the ammonia values increase beyond the normal figures in the acute attacks. This would bring gout into analogy with other acute febrile processes, and would not point without further evidence to a specific gouty anomaly of metabolism.

(*d*) *Hippuric Acid.*

Lewin (105) found in two cases of gout 0·118 to 0·157 and 0·16 to 0·19 gramme of hippuric acid in the urine. These values agree with those which he obtained in healthy subjects under similar dietary restrictions.

(*e*) *Urobilin.*

According to Magnus-Levy (3), the urobilin content of the urine is frequently increased during the acute attack. I can confirm this from my own experience. We must refer this to hæmolytic processes. The phenomenon proves that toxic influences play a rôle in the acute attack. No quantitative determinations of urobilin are extant.

3. Acidity.

That the acidity of gouty urine is—at least, at times—abnormally high is an old doctrine, and stands in close relationship to the theories of gout. It is also brought into association with Pfeiffer's teaching of the easier separability of the uric acid by the uric acid filter. Investigations which have been carried out with trustworthy methods are few in number. Camerer (106) states that the acidity of gouty urine seemed to him to be somewhat higher than normal. Soetbeer (107) published a very exact analysis, according to which the urine of a gouty patient contained an excess of 0·44 gramme of acid over the bases, while in the control urine of a healthy subject the alkali (calculated as sodium) was 0·6 to 0·9 gramme in excess. A. P. Luff (58A) found normal acidity values in a case of subacute gout (acidity of twenty-four hour specimen, 0 to 1·629 gramme HCl). No parallelism can be recognised between the reaction of the urine and the alkalinity of the blood. I have at my disposal a few personal observations on this subject. By the use of Lieblein's method in the cases of three gouty patients I found during the attack that the relations of di-sodium-phosphate to monosodium phosphate were 1 : 1, 1 : 1·25, and 1 : 1·27. These are normal values, which appear very often among the normal figures of Strauss (109).

4. Salts of the Urine.

Among the inorganic salts of the urine the phosphates have almost exclusively engaged the attention of writers. To-day no further importance is attached to the older data regarding the increase and decrease of phosphoric acid in the course of gout (110), because the phosphoric acid intake was entirely neglected. Moreover, the numerous works of more recent investigators [Ebstein, Camerer senr., Weintraud, Pfeiffer (111)], as well as the metabolic investigations of Umber, Schmoll, and Waldvogel (112), have taught us nothing of importance, although the phosphoric acid intake remained for a longer time practically constant. No definite relation has been established between the phosphoric acid excretion and

the phase of the gouty process. A new point of view was presented by the researches of Loewi and Vogt (113). They found that, on addition of nuclein to a constant diet, the phosphoric acid of the nuclein was promptly excreted, but the nitrogen was retained. The conclusions which were drawn regarding the theory of gout, and especially of the nuclein decomposition and of the retention of purin substances in the body of the gouty, were, however, again upset by the investigations of Kaufmann and Mohr (10), who were the first to work out the actual phosphoric acid balances of the gouty. In their cases the relation between the excretion of nitrogen and of phosphoric acid was found to lie within normal limits. They were, further, able to show that our knowledge regarding the fate of phosphoric acid in the body does not suffice to permit us to draw far-reaching conclusions from such findings.

Importance is also often attached to the relation of the earthy phosphates to the alkali phosphates. The normal quotient of 1 : 2·5 is extended in the cases of Stocvis (110) to 1 : 5·7. In the three cases of Ebstein (111) the relations were 1 : 1·7, 1 : 1·5 to 2·7, 1 : 3 to 4·1. Here also we must be satisfied to simply record the facts. It is so much the less possible to draw conclusions from these findings, as absolutely no figures are known which refer at the same time to phosphoric acid and the earthy phosphates in metabolic experiments.

The statement of Reale (114) that, on boiling the urine of a gouty patient with acetic acid, crystals of calcium sulphate are frequently precipitated is worthy of mention. I have sought for this reaction in a large number of cases of gout, but have never been able to obtain a positive result. Perhaps the kind of diet may be a determinative factor in the outcome of this reaction.

5. Oxalic Acid.

Garrod found oxalic acid in the blood of gouty patients. On this account, and because of the conversion of uric acid into allantoin, and, further, into oxalic acid and urea (the conversions are brought about in alkaline solution under the influence of oxidizing agents), pathological variations in the excretion of oxalic acid are conceivable in gout. Only one exact investigation—that of Mohr and Salomon (115)—is at hand. A man who had suffered for many years with articular gout excreted, on a mixed hospital diet, 4·4 to 7·1 milligrammes of oxalic acid. These figures lie at the lower limit of the values found in healthy subjects under the same dietary conditions.

6. Sugar.

It is known that gout and diabetes are often present in the same individual. There is much discussion regarding the frequency of this combination [one may compare Minkowski's figures (1)]. In France the coincidence of these two diseases seems to be especially frequent. According to my own extensive statistics of the year 1901, the presence of

gout was shown in only 3 per cent. of diabetics. By reference to the cases (about 600) of diabetes observed since then, the percentage is slightly increased. My figures are, however, far below those of Grube (116). I must declare myself as absolutely opposed to the statement, which frequently recurs in earlier writings, that diabetes and gout frequently alternate in the same individual. The old assertions are traceable to the facts that mild glycosuria disappears and gouty complaints develop on a diet rich in meat, while, *vice versa*, glycosuria again appears and the gout subsides on a diet poor in meat and rich in carbohydrate. If a true alternating type of both diseases has been observed independently of the diet, this can be, judging from the unusually large material from which I have drawn during ten years, only the rarest exception.

Relying upon the old reports, workers have frequently investigated the question as to how gouty patients react to intake of sugar—that is to say, does an alimentary glycosuria occur more easily in them than in healthy subjects ? Strauss (117) observed, in four out of six cases, alimentary glycosuria after an intake of 100 grammes of grape-sugar. However, the patients which he examined were partly alcoholic and partly obese subjects, who were thus already predisposed to alimentary glycosuria even in the absence of gout. Magnus-Levy (3) reported, without any details, two positive results out of five experiments. According to Badt (118), who brings forward the most extensive material, alimentary glycosuria is extremely rare in gout. Out of sixteen gouty patients, only one, who was afflicted with obesity at the same time, showed a glycosuria following the intake of 100 grammes of grape-sugar. My own observations agree with this. I found in all the gouty subjects who were treated during the last ten years in my hospital wards glycosuria no more frequently and of no higher grade than occasionally appears in healthy subjects after feeding with sugar. This refers as well to experiments with glucose as to those with cane-sugar and lævulose. Only in cases in which pronounced chronic alcoholism complicated the condition were the excretions of sugar found to be higher and more frequent.

7. Albumin.

Albumin is often found in small amounts at the commencement of the attack. It may be partly a question of febrile albuminuria. Yet the paroxysm, with its severe pain, furnishes abundant cause for disturbances of the circulation, so that for this reason also albuminuria may be brought about. If albuminuria is observed in typical or atypical cases of gout during the attack-free periods, then it must always be a question of an accompanying organic disease of the kidney. Regarding the relations of nephritis to gout, see Index.

8. Albumoses.

I once found albumoses in the urine, which was collected during the fifth and last day of a severe attack, by Hofmeister's old method. This calls to mind other forms of albumosuria which appear if fragments

of tissue are quickly absorbed, and likewise brings up the question of the well-recognised febrile albumosuria (see Vol. II.). The methods which were used are not considered to-day absolutely free from objections. New investigations are much to be desired.

VII.—THEORY OF GOUT.

It is not to-day very alluring to write anything regarding the theory of gout, especially in a book which is essentially devoted to the presentation of facts. All of the theories advanced up to the present time have fared badly. The positive material is much too insufficient and too ambiguous.

The important points to which we must cling are the following :

1. The acute attacks of gout show distinct toxic characteristics. Nothing speaks for the assumption that the toxic substance is introduced into the body from without ("exogenic toxicosis," as in infectious diseases); everything points to its being of endogenous origin. The statement that gout is an endogenous anomaly of metabolism will not now be opposed. Likewise we can easily agree with those who look for the primary localization of the disease in the kidney (specific insufficiency of the renal epithelium as regards the excretion of uric acid). It is only with those who have so little clinical experience that they presuppose an ordinary nephritis as the cause of such insufficiency that we cannot come to terms.

2. The more exact investigations of the purin metabolism continue to enhance the value of Sir A. Garrod's observation that retention of uric acid is present in gout. I call to mind the universally lower values for the elimination of endogenous uric acid, the remarkably large variations in this elimination, and the delayed reaction of the urine to intake of purin bodies, which condition does not obtain at all times nor in every stage of a constitutional anomaly. We must assume a directly increased fermentative decomposition of the purin bodies—that is, an increased uricolysis—if we do not wish to explain the low, long-continued, diminished uric acid excretion by a retention. There is no evidence to indicate an increase of uricolysis in gout. Finally, the uric acid content of the blood and the accumulation of uric acid in the tophi may also be interpreted as retention phenomena. In this acceptation it remains uncertain whether the retention arises because the outlet (kidneys) is blocked, or because the uric acid is held fast by chemical affinities.

I consider it of practical importance to insist, as a physician, on the point that gouty patients have a tendency to uric acid retention—that is, the uric acid which they form is excreted less easily than is the case with healthy subjects. This has the following therapeutic consequences : In the first place, we make use of measures which are intended to facilitate the excretion of uric acid in the urine. In this regard we very quickly reach the limits of therapeutic possibility. Secondly, we regulate the

intake of food so that the formation of uric acid is diminished. This is not necessary to the same extent at all times, because the gouty subject has periods in which he excretes uric acid exceedingly well. I showed, in collaboration with my former assistant, Schliep (119), how it was possible to determine the eliminative power of the gouty subject for uric acid. This resolved itself into an estimation of the tolerance of the patient for nucleins (see similar method for carbohydrates in diabetes). Naturally, it must not be imagined that the metabolic disorder of gout can be cured in this way. It is only a means of carrying out a very rational functional therapy. It enables the road to be cleared of obstacles over which the organism could not pass alone, just as in cardiac patients the limit of the reduced mechanical power of the heart is carefully determined. We may, perhaps, hope to gradually improve the general condition by such a " sparing " of the purin metabolism. Experience seems to point in this direction.

3. The finding of Bloch (51B) that uric acid exists in the blood in two different combinations is extremely important. It supports the hypothesis of Minkowski (1) that uric acid remains in the body of the gouty subject because its compounds are not sufficiently capable of being transported and excreted in the urine. In this connection I think less of the lack of uric acid binding receptors—if one may use an expression derived from the theory of immunity—than of an anomaly of fermentation. We now know how great a part the ferments play in purin metabolism. If a ferment which converts uric acid into compounds which are easily soluble, easily transportable, and at the same time easily excreted in the urine, is lacking, or is present in insufficient amounts, then many peculiarities of gout are intelligible. However, not all of the phenomena, especially the paroxysmal character of the disease, can be thus explained. On the contrary, the anomaly of fermentation would be just as compatible with the assumption of an endogenous character of gout as with the autotoxic, inflammatory, and febrile phenomena of the disease.

We have proof that uric acid is present in the blood in different forms. In one the uric acid exists as a salt, in the other as a firm combination with some as yet unknown substance. As soon as it was proven that these two forms differed as to their solubility, capability of being transported, and capability of being excreted in the urine, and, further, after the proof was forthcoming that the more difficultly soluble, transportable, and "excretable " uric acid was in excess in the blood and tissues, then we were justified in advancing the following conceptions :

Deviations from the normal relations can take place in three directions.

1. The forces (ferments ?) which transform the uric acid into its " excretable " form are normal, but the supply of uric acid to the blood is so great that a certain proportion remains untransformed. Therefore a part of the uric acid remains in the blood—as, for instance, in pneumonia, leuchæmia, and in excessive feeding with nuclein.

2. The formation of " excretable " uric acid and its passage into the blood are normal, but the kidneys are less capable of reacting, and with-

draw the uric acid from the blood only when the acid reaches a definite higher concentration (in nephritis, and perhaps, also, as a result of a specific gouty functional disturbance of the renal epithelium).

I would like, in this place, to just touch upon the question whether we must actually regard all and every uric acid deposition as gouty in character. If the views which are here expressed are correct, one can admit that the continuous overloading of the blood with uric acid, as is observed in chronic nephritis, may lead to deposition of urates in specially favoured places—that is, in places such as the metatarso-phalangeal joint of the great toe, where the circulation is slow. This would have nothing to do with pure gout, for only the anatomical end-results are identical. The ætiology and the pathogenesis are quite otherwise. The relations are somewhat on a par with alimentary and diabetic glycosuria. The chemical analysis of the urine and the blood give the same findings, glycosuria and hyperglycæmia. However, the pathogenesis of the two processes is fundamentally different. The one depends on more artificial and more casual overloading of the blood; the other is dependent on a severe anomaly of metabolism.

3. The forces (ferments ?) which transform uric acid into easily soluble and "excretable" compounds are weakened. This would be an anomaly of metabolism, and, indeed, a characteristic anomaly of gout, which is present in no other disease.

It will be the next and most fruitful problem of the investigation of gout to make clear the true combining relations of the circulating uric acid, both in the healthy and gouty subject. The theory of gout will obtain a sure foundation only when this preliminary question is decided.

LITERATURE.

1. Minkowski: Die Gicht, in Nothnagels Spez. Pathol. u. Ther. VII. 1903.—Wiener: Die Harnsäure in ihrer Bedeut. für die Pathol. Er. Ph. **1903.** I. 377.

2. Bouchard: Les mal. par ralentissement de la nutrition. 1890; and Troubles préalables de la nutrition. 1900.

3. Magnus-Levy: Ueber Gicht. Z. M. **36.** 353. 1899.

4. Ebstein: Vererbbare zelluläre Stoffwechselkrankh. 1902.

5. v. Noorden: Ueber Gicht. V. p. G. 17. II. 1893.—Vogel: Ueber Gicht, in v. Noorden's Beitr. zur Lehre vom Stoffw. **2.** 113. 1894.

6. v. Noorden: Lehrb. der Path. des Stoffw. P. 429. 1893.

7. Schmoll: Stoffwechselvers. an einem Gichtkranken. Z. M. **29.** 510. 1896.—Schmoll: Einige Bemerk. zur Theorie der Gicht. C. i. M. **1898.** 1065.—Magnus-Levy: Stoffw. bei Gicht. B. k. W. **1896.** Nr. 18, and Lit. Nr. 3.—Leber: Zur Physiol. und Pathol. der Harnsäureaussch. B. k. W. **1897.** Nr. 44, 45.—Watson: General Metab. in Gout. B. M. J. **1900.** 1. 10.—Laquer: Ueber die Ausscheidungsverhält. der Alloxurkörper. V. C. M. **14.** 333. 1896.—Zagari e Pace: La genesi dell' acido urico e la gotta. 1897.—Reach: Stoffw. der Gicht. Mü. m. W. **1902.** Nr. 29.—Vogt: Ein Stoffwechselver. bei akuter Gicht. D. Ar. M. **71.** 21. 1901.—Kaufmann u. Mohr: Alloxurkörperfrage u. zur Pathol. der Gicht. D. Ar. M. **74.** 141, 348, 586. 1902.—Brugsch: Zur Stoffwechselpath. der Gicht. Z. e. P. **2.** 619. 1906.

8. Soetbeer u. Ibrahim: Ueber das Schicksal eingeführter Harnsäure im menschl. Organ. Z. p. C. **35.** 1. 1902.

9. Zagari: Il Balancio organ. di un gottoso durante e fuori l'accesso. P. **6.** 89, 162. 1899.

10. Kaufmann u. Mohr: Lit. Nr. 7. P. 594.

11. Loewi: Nukleinstoffwech. E. A. **44.** 1. 1900.—Hager: Zur Pathogen. der Gicht. Mü. m. W. **1900.** 1011.—Vogt: Lit. Nr. 7.

12. Soetbeer: Ein Stoffwechselver. bei Gicht. Z. p. C. **50.** 55. 1904.

13. Pfeiffer: Die Gicht und ihre Behandl. 1891.

14. Soetbeer: Ueber den Einfl. der Nahrungsaufnahme auf die Aussch. der Harnsäure bei Arthritis urica. Z. p. C. **40.** 25. 1904. — Vogt, Kaufmann u. Mohr, Reach: l. c. (7).

15. Weintraud: Ueber Harnsäurebild. beim Menschen. D. A. **1895.** 382. B. k. W. **1895.** 405.

16. Grube: Ueber gicht. Erkrankungen des Magens. V. C. M. **18.** 189. 1900.

17. Falkenstein: Ueber das Wesen der Gicht und ihre Behandl. D. m. W. **1904.** 57.

18. Edinger: Bedeut. der Rhodanverbind. für den Organismus. D. m. W. **1903.** Nr. 29.

19. Falkenstein: Ueber das Verhalt. der Harnsäure und des Harnstoffs bei Gicht. B. k. W. **1906.** 228.

20. Oechsner de Coninck: C. r. S. B. **50.** 298. 1898.

21. Grossmann: Zur Kenntnis des Harnsäurestoffw. des Harnindikans bei Gichtkranken. B. k. W. **1903.** Nr. 24.

22. v. Noorden u. Ritter: Stoffw. der Nierenkranken. Z. M. **19.** 197. Suppl. 1891.

23. Petrén: Vorkommen, Menge und Abstammung der Xanthinbasen in den Fäzes. Sk. Ar. P. **7.** 315. 1898.

24. Walker Hall: A Contrib. to the Knowledge of the Purin Bodies of Human Fæces. J. P. and B. **9.** 246.—Krüger u. Schittenhelm: Die Purinkörper der menschl. Fäzes. Z. M. **35.** 153. 1902; **45.** 14. 1905.—Schittenhelm: Die Purinkörper der Fäzes. D. Ar. M. **81.** 423. 1904.

25. Strasburger: Über die Bakterienmenge in menschl. Fäzes. Z. M. **46.** 425. 1902.—Schittenhelm u. Tollens: Über den quant. Anteil der Bakterien an Stickstoff und Purinbasen der Fäzes. C. i. M. **1904.** Nr. 30.

26. Garrod: Nature and Treatment of Gout. 1861 (English and German). Würzburg.

27. Lehmann: Physiol. Chemie. I. 221. 1850.—Ranke: Über Ausscheid. der Harnsäure. 1858.—Braun: Beitr. zu einer Monographie der Gicht. I. Heft. 1860.—Lécorché: Traité de la goutte. 1884.—Cantani: Oxalurie, Gicht, Steinkrankh. 1880.—Bartels: Ueber die Ursachen einer gesteigerten Harnsäureaussch. D. Ar. M. **1.** 1. 1866.

28. Burian: Die Bild. der Harnsäure im Organ. des Menschen. M. K. **1905.** P. 130.—Die Herkunft der endogenen Harnpurine. Z. p. C. **43.** 532. 1905.

29. Wiener: Synthet. Bildung der Harnsäure im Tierkörper. Be. P. P. **2.** 42. 1902.

30. Schittenhelm: Ueber die Fermente des Nukleinstoffw. Z. p. C. **43.** 228. 1904.

30a. Schittenhelm: Lit. Nr. 30 and 32.

30b. Jones u. Partridge: Ueber die Guanase. Z. p. C. **42.** 343. 1904.—Jones u. Winternitz: Ueber die Adenase. Ibid. **44.** 1. 1905.

31. Schittenhelm: Der Nukleinstoffw. u. seine Fermente. Z. p. C. **46.** 354. 1905.

32. Spitzer: Die Ueberführung der Nukleinbasen in Harnsäure. Ar. P. M. **76.** 192. 1899.—Wiener: Ueber Zersetzung u. Bildung der Harnsäure. E. A. **42.** 373. 1899.—Schittenhelm: Ueber die Harnsäurebild. in Gewebsauszügen. Z. p. C. **42.** 251. 1904 and Nr. 30.—Ueber Harnsäurebild. und Harnsäurezersetz. Z. p. C. **45.** 121. 1905.—Burian: Ueber die oxydative und die vermeintl. synthet. Bildung von Harnsäure im Rinderleberauszug. Z. p. C. **43.** 497. 1905.

33. Wiener: Nr. 32.—Ascoli: Ueber die Stellung der Leber im Nukleinstoffw. Ar. P. M. **22.** 340. 1898.—Schittenhelm: Burian, Lit. Nr. 32.

34. Schittenhelm: Ueber das urikolytische Ferment. Z. p. C. **45.** 161. 1905.—Wiener: Ueber Harnsäurezersetz. durch Organferment. C. P. **18.** 690. 1905.

35. Burian u. Schur: Ueber die Stellung der Purinkörper im menschl. Stoffw. Ar. P. M. **80.** 241. 1900; und das quant. Verhalten der menschl. Harnpurin-

aussch. Ibid. **94.** 273. 1902.—Walker Hall: The Purin Bodies of Foodstuffs. 1902.—Sivén: Zur Kenntnis der Harnsäurebild. Sk. Ar. P. **11.** 123. 1900.—Kaufmann u. Mohr: Nr. 7.—Rockwood: The Elimination of Endogenous Uric Acid. A. J. P. **12.** 38. 1904.—B. Bloch: Lit. Nr. 36a.

36. Burian u. Schur: Nr. 32. P. 310 (1902).—Walker Hall: Lit. Nr. 35.

36a. Rzentkowski: Zur Frage der Alloxurkörperaussch. unter dem Einfluss des Fleischgenusses. Ar. V. **11.** 440. 1905.—Bloch: Zur Kenntnis des Purin-Stoffw. beim Menschen. D. Ar. M. **83.** 499. 1905.

37. Pfeiffer: Ueber Harnsäure und Gicht. B. k. W. **1892.** Nr. 16-21.—Ebstein u. Spraque: Beitr. zur Lehre von der harnsauren Diathese. 1891.—Vogel: Nr. 5.—Magnus-Levy: Nr. 7.—His: Die Ausscheid. der Narnsäure im Urin der Gichtkranken. D. Ar. M. **65.** 156. 1900.—Badt: Harnsäure oder Alloxurdiathese. Z. M. **34.** 359. 1896.—Watson: Lit. Nr. 7.

38. Pfeiffer: Zur Aetiol. und Ther. der harnsauren Steine. V^th^ V. C. M. **1886.** 444.—Harnsäureaussch. und Harnsäurelösung. VII. V. C. M. **1888.** 337.—Die Natur und Behandl. der Gicht. VIII. V. C. M. **1889.** 166.—Die Gicht und ihre Behandl. 1891.

39. Ebstein u. Spraque: Lit. Nr. 37.—v. Noorden: Referat über Gicht. B. k. W. **1893.** P. 1221.—Pathol. des Stoffw. P. 434. 1893.—Roberts: Chem. and Therap. of Uric Acid Gravel and Gout. 1892.—Minkowski: Lit. Nr. 1.

40. Kolisch: Ueber Wesen und Behandl. der uratischen Diathese. 1895.

41. Zülzer: Ueber die Alloxurkörperaussch. bei Nephritis. B. k. W. **1896.** 69.

42. His: Untersuch. an Gichtkranken. Ibid. **1896.** 970.

42a. Kaufmann u. Mohr: Lit. Nr. 7.—Walker Hall: Lit. Nr. 44.—Benjamin: Ueber Purinbasen-Ausscheid. Salkowski-Festschr. S. 61. 1904.

43. Laquer: Lit. Nr. 7.—Strauss: Pathogen. und Ther. der Gicht. W. Ab. II. H. 8. 1902.—Grossmann: Lit. Nr. 21.—Brugsch, Kaufmann u. Mohr: Lit. Nr. 7.—v. Noorden u. Schliep: Ueber intermit. diätet. Behandl. der Gicht. B. k. W. **1905.** Nr. 41.

44. Walker Hall: The Chem. Path. of Gout. B. M. J. 24 Sept., 1904.—Gouty Urines. B. M. J. 1906.—Purin Bodies. 1902. P. 124.

45. Leber: Lit. Nr. 7.—Escheburg: Zur Kenntnis der Harnsäureaussch. bei Gicht. Mü. m. W. **1905.** Nr. 47.—Weintraud: Beitr. zum Stoffw. der Gicht. Ch.-An. **1895.** 275.—Magnus-Levy: Lit. Nr. 3.—Rommel: Die Ausscheid. der Alloxurkörper bei Gicht. Z. M. **30.** 200. 1896.

46. Pfeiffer: Lit. Nr. 38.—Ueber Harnsäure und Gicht. B. k. W. **1892.** Nr. 16, 17, 19, 20, 21.—Ueber die Ausscheid. im Urin während des akuten Gichtanfalles. B. k. W. **1896.** 319.

47. Ebstein: Nr. 37.—Vogel: Nr. 5.

48. v. Noorden: Nr. 6. P. 436.

49. His: Untersuch. an Gichtkranken. W. m. B. **1896.** 291.—Die Ausscheid. der Harnsäure im Urin Gichtkranken. D. Ar. M. **65.** 156. 1900.—Magnus-Levy: Nr. 3.

50. Weintraud: Ueber Harnsäure im Blute. W. k. R. **1896.** Nr. 1, 2.

51. Strauss: Ueber die Beeinflussung der Harnsäure-Ausscheid. durch die Extraktivst. des Fleisches. B. k. W. **1896.** 710; und (über Blut) die chron. Nierentzündungen. 1902. P. 108.

51a. Schur: Die Bedeut. der Harnsäure in der Path. des Stoffw. W. m. P. **1906.** Nr. 3, 4.

51b. Bloch: Zur Kenntnis des Purinstoffwech. beim Menschen. Ar. M. **83.** 499. 1905.

52. Garrod: Nr. 26. P. 52.

53. Salomon: Ueber pathol.-chem. Blutuntersuch. Ch.-An. **5.** 139. 1880.

54. Klemperer: Zur Path. und Ther. der Gicht. D. m. W. **21.** 655. 1895.

55. Bence-Jones: Gravel Calculus and Gout (English and German). 1845.—Charcot: Léc. clin. sur les maladies des vieillards. 1874.—Ranke: l. c. (No. 27).—Dyce Duckworth: Gout (English and German). 1894.

56. Haig: Microsc. Detection of the Uric Acid in the Blood. L. **1898.** 860. Haig: Uric Acid. 1902 (English and German).

57. Luff: L. **1898.** 860.

58. Klemperer: Ueber einige Fermentwirkungen des menschl. Blutes. Leyden-Festschr. II. 1902, and C. i. M. **1904.** Nr. 52.

58a. Trenkner: Ueber das Harnsäure-Lösungsvermögen von Blutserum.

C. i. M. **1904.** Nr. 45.—Ritter: Bedingungen für die Entstehung von Harnsäuresedimenten. Z. B. **35.** 155. 1897.—Levison: Die Harnsäurediathese. 1893.—Levison: Pathogenese der Gicht. Z. M. **26.** 293. 1894.—Levison: Die Harnsäure als Krankheitsursache. Ar. V. **3.** 478. 1898.—Luff: Pathology and Treatment of Gout. 1900 (English and German).—Strauss: Nr. 51 (1902).

58b. Taylor: Solubility of Uric Acid in Blood-serum. J. B. C. **1.** 177. 1906.

58c. Farkas: Ueber die Konzentration der Hydroxylionen im Blutserum. Ar. P. M. **98.** 551. 1903.—Höber: Ueber die Hydroxylionen des Blutes. Ibid. **99.** 572. 1903.—Fränkel: Methode zur Bestim. der Reaktion des Blutes. Ibid. **96.** 601. 1903.

59. Minkowski: Nr. 1. P. 203.

60. Minkowski: V. C. M. **1900.** 439 and Nr. 1. P. 205.

61. Goto: Ueber die Lösung der Harnsäure durch Nukleinsäure. Z. p. C. **30.** 473. 1900.

62. His: Die harnsauren Ablagerungen des Körpers u. die Mittel zu ihrer Lösung. T. G. **3.** 434. 1901.

63. Schittenhelm u. Bendix: Ueber das Schicksal der in die Blutbahn eingebrachten Nukleinsäure. D. m. W. **1904.** Nr. 32.

64. Ebstein u. Spraque: Beitr. zur Anal. gichtischer Tophi. Ar. p. A. **125.** 207. 1891.

64a. Almagia, Pfeiffer: Zur Lehre von Harnsäure-Stoffwechsel. Be. P. P. **7.** 459, 463, 466. 1905.

65. Ebstein: Die Natur und Behandl. der Gicht. 1882.—v. Leyden's D. K. III. 98. 1902.—v. Loghem: Betrachtungen über einen atypischen Fall von Gicht. P. W. **1904.** Nr. 36, 37.

66. Freudweiler: Über das Wesen der Gichtknoten. D. Ar. M. **63.** 266. 1899.—Über die Entstehung der Gichtknoten. Ibid. **69.** 155. 1901.

67. Naunyn: Ueber die Chemie der Transsudate und des Eiters. D. A. **1865.** 266.—Pickardt: Zur Kenntnis der Chemie path. Ergüsse. B. k. W. **1897.** Nr. 33.

68. v. Noorden: Nr. 6. P. 439.—Likhatscheff: Über die Ureterenunterbindung bei Hühnern, etc. Be. A. P. **20.** 102. 1896.

69. Klemperer: Nr. 54.—Strauss: Nr. 51 (1902).—Freudweiler: Nr. 66 (1901).

69a. Loghem: Experimentelles zur Gichtfrage. D. Ar. M. **85.** 416. 1905.

70. v. Noorden: Nr. 6. P. 439.

71. Pfeiffer: Die Gicht. P. 42. 1891.

72. Jeffries: The Reaction of the Blood. B. M. & S. J. **120.** 503. 1889.—Drouin: Hémoalcalimétrie. P. 169. 1892.

73. Klemperer: l. c. (54).—Magnus-Levy: (3).—Strauss: Ueber das Verhalten der Blutalkaleszenz des Menschen. Z. M. **30.** 317. 1896.—Watson: General Metab. and the Blood in Gout. B. M. J. **1.** 10. 1900.—Luff: Alkalinity of the Blood in Gout. Ibid. **1.** 1066. 1898.—Loewy: Ueber die Alkaleszenzverhält. des menschl. Blutes. C. m. W. **1894.** 785.

74. Mordhorst: Ueber Fleischnahrung bei Gicht. V. C. M. **12.** 499. 1893.

75. v. Noorden: Neue Arbeiten über Gicht. B. k. W. **1893.** 1221.

76. v. Noorden: Nr. 6. P. 439.

77. Rindfleisch: Ueber Bildung und Rückbild. gichtischer Tophi. Ar. p. A. **171.** 361. 1903.

77a. Loghem: Sur la résorp. de l'acide urique et de l'urate de soude. An. P. **1904-1906.**

78. Roberts: The Chem. and Therap. of Uric Acid Gravel and Gout. B. M. J. **1892.** 1. 1285, 1347. II. 6, 61.

79. Mendelsohn: Problem der Harnsäureauflösung. D. m. W. **1895.** Nr. 18.

80. His: Über das Verhalten der Harnsäure in Lösungen. V. C. M. **18.** 427. 1900.—Klemperer: Beitr. zur Erklärung harnsäurer Niederschläge im Urin. Z. d. p. T. **5.** 48. 1901.—Loghem: Lit. Nr. 69a.—His u. Paul: Über das Verhalt. der Harnsäure und ihrer Salze in Lösungen. Z. p. C. **31.** 1 and 64. 1900.

80a. Kionka u. Frey: Beitr. zur Kenntnis der Gicht. Z. e. P. **2.** 1. 1905.—Kionka: Entstehung und Wesen der Gicht. D. m. W. **1905.** Nr. 29.—Abderhalden u. Schittenhelm: Bemerkungen zu den Arbeiten von Frey. Z. e. P. **2.** 1905.—Ignatowski: Lit. Nr. 103.—Lipstein, Fossnar: Lit. Nr. 104.

81. Schreiber u. Zaudy: Ueber die bei Vögeln künstlich zu erzeugenden Harnsäureablagerungen. Ar. P. M. **79.** 53. 1900.

82. Riehl: Zur Anat. der Gicht. W. k. W. **1897.** 761.—Freudweiler: Nr. 66 (1901).—Rosenbach: B. k. W. **1904.** 510.—Litten: Ibid. P. 509.—Aschoff: Histol. Untersuch. über Harnsäureablagerungen. V. D. G. **1899** and **1900.**

83. Krause: Zur Kenntnis der Uratablagerungen im Gewebe. Z. M. **50.** 136. 1903.—Minkowski: l. c. (1).

84. Goto, His, Minkowski: Nr. 60-62.

85. Garrod: Nr. 26. P. 71.

86. Lehmann: l. c. (27). I. 223.—Bouchard: l. c. (2). P. 266.—Martini e Ubaldini: Rech. sur la compos. de la sueur d'un goutteux. P. m. b. **1866.** Nr. 41.

87. Kühne: Physiol. Chemie. P. 435. 1868.

88. Tichborne: On the Elimination of Uric Acid by the Skin. B. M. J. **1887.** II. 1097.

89. Boucheron: C. r. S. B. 4 Mai, 1896.

90. Hayem: cit. by Minkowski: l. c. (1). P. 96.

91. Magnus-Levy: Lit. Nr. 3.

92. Garrod: l. c. (26). P. 51 u. 60.

93. Grawitz: Beobacht. über ein neues harnsäurelösendes Mittel. D. m. W. **1894.** Nr. 14.—v. Limbeck: Klin. Path. des Blutes. P. 348. Jena, 1896.

94. Ten Cate: Beitr. zur gicht. Diathese. Diss. Götting. 1899.

95. Milroy and Malcolm: Metab. of Nucleins. J. P. **23.** 217. 1898.

96. Neusser: Ueber einen besonderen Blutbefund bei uratischer Diathese. W. k. W. **1894.** 727.

97. Futcher: Ueber den Zusammenhang zwischen der sog. perinukleären Basophilie und der Aussch. der Alloxurkörper im Harn. C. i. M. **1896.** 985.

98. Ehrlich u. Lazarus: Die Anämie. P. 28. 1898.

99. Waldvogel: Der Stoffw. im Gichtanfall. C. S. 3. 1. 1902.—Strauss: l. c. Nr. 51. P. 69.

99a. Strauss: Gicht u. Tuberkulose. B. K. T. **2.** 365. 1905.

100. Garrod: Nr. 26. S. 66.

101. Camerer: Gesamt-N, Harnstoff, Harnsäure und Xanthinkörper im menschl. Harn. Z. B. **28.** 72. 1891.

102. Boedtker: Beitr. zur Kenntnis des Eiweissabbaues im menschl. Organismus. 1896.

103. Ignatowski: Vorkom. von Aminosäuren im Harn, besonders bei Gicht. Z. p. C. **42.** 371. 1904.

104. Embden u. Reese: Ueber die Gewinnung von Aminosäuren aus normal. Harn. Be. P. P. **7.** 411. 1905. — Lipstein: Die Ausscheid. der Aminosäuren bei Gicht und Leukämie. Be. P. P. **7.** 527. 1905.—Fossnar: Ueber das Vorkommen von freien Aminosäuren im Harn. Z. p. C. **47.** 15. 1906.—Walker Hall: B. J. 1906. P. 241.

105. Lewin: Beitr. zum Hippursäurestoffw. Z. M. **42.** 371. 1901.

106. Camerer: Der Gehalt des menschl. Harns an N-haltigen Körpern. P. 28. 1901.

107. Soetbeer: Ein Stoffwechselver. bei Gicht. Z. p. C. **50.** 55. 1903.

108. Lieblein: Ueber die Bestim. der Azidität des Harns. Z. p. C. **20.** 52. 1895.

109. Strauss: Ueber die Einwirk. des kohlensauren Kalks auf den Stoffw. Z. M. **31.** 493. 1897.

110. Stocvis: Zur Kenntnis der P_2O_5-Aussch. bei Arthritis. C. m. W. **1875.** 801.—Bouchard: l. c. (2). P. 271.—Berthollet u. Scudamore, quoted by Bouchard.

111. Ebstein: Beitr. zur Lehre von der harnsauren Diathese. P. 142. 1891.—Camerer: Lit. Nr. 101.—Weintraud: Beitr. zum Stoffw. in der Gicht. Ch.-An. **20.** 215. 1895.—Pfeiffer: Lit. Nr. 46 (**1896**).

112. Waldvogel: Der Stoffw. im Gichtanfall. C. S. **3.** 1. 1902.—Umber: Einfl. nukleinhalt. Nahrung auf die Harnsäurebild., in Klemperer's Untersuch. über Gicht und harnsaure Nierensteine. S. 16. 1896.—Schmoll: l. c. (7).

113. Loewi: Zur Kenntnis des Nuklein-Stoffwech. E. A. **44.** 1. 1901.—Vogt: l. c. (7).

114. Reale: Sulfate de chaux dans les urines des arthritiques. Se. m. **1903.** 368.

115. Salomon u. Mohr: Zur Phys. und Path. der Oxalsäurebild. und Ausscheid. D. Ar. M. **70.** 486. 1901.

116. Grube: Zur Aetiol. des sog. Diab. mell. Z. M. **27.** 465. 1895.

117. Strauss: Ueber den Einfl. verschied. Zuckerarten auf die Zuckeraussch. B. k. W. **1898.** 398 u. 420.

118. Badt: Ueber die Reaktion der Gichtkranken auf Traubenzucker. Ct. P. S. **1906.**

119. v. Noorden u. Schliep: Ueber individualisierende diätet. Behandl. der Gicht. B. k. W. **1905.**—Walker Hall: Clinical Estimation of Gouty Urines. B. M. J. 1906.—W. Bain: B. M. J. 1898, 1900.

CHAPTER III

OBESITY

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Translated by D Spence, Ph.D.

I.—THE ENERGY EXCHANGE.

Obesity is the result of a long-continued disproportion between the amount of fat consumed and that metabolized. It has already been pointed out that protein may be retained in the body, and may therefore be regarded as a source of gain, although the amount of such protein is usually small, and only becomes large when the calorific value of the food-supply is enormously increased, or when, for other reasons, an energetic cell growth occurs. With this exception, by far the greater part of that food which is not required for the immediate wants of the tissues goes to enrich the fat depots; indeed, often the entire quantity of this excess food is thus deposited, the protein remaining practically the same [Pflüger (1)]. Leaving from our consideration, therefore, the deposition of protein—which only takes place under favourable conditions—the following facts remain:

The ingestion of a quantity of food greater than that required by the body leads to an accumulation of fat, and to obesity should the disproportion be continued over a considerable period.

From this it follows that obesity may occur as the result of—

1. An increased food-supply with normal energy expenditure.

2. A normal food-supply with diminished energy expenditure. Here one must distinguish between expenditure of energy diminished on account of muscle inactivity and that diminished as the result of a diseased condition of the cells of the body, whereby the oxidation processes are carried out less energetically—*i.e.*, a slowing of metabolism.

3. A combination of both conditions.

The extent to which these factors are severally instrumental in causing the various clinical forms of obesity is a question to be dealt with in the special works on pathology [von Noorden (2)]. Here we have only to consider the question whether or not a form of obesity exists which is the result of a diminution in the energy of protoplasmic decomposition, which may therefore be regarded as the result of abnormal metabolism.

1. Obesity Associated with Normal Expenditure.

Clinical experience has shown beyond all doubt that when the amount of actual energy expenditure lies within the normal limits, obesity is due to a long-accustomed but excessive intake of food. The amount of food consumed, and the nature of that food, afford valuable indications of obesity from such a cause. Such obese individuals frequently prefer fat-forming or carbohydrate food in which a high calorific value is combined with small volume.

As a rule it is the natural inclination on the part of every human being to maintain his state of nutrition at a constant level, this level being determined by his own free will—that is to say, he regulates his food-supply without any precise regard to the actual requirements of his tissues. Equilibrium is not, of course, maintained at every hour of his life ; at one time, perhaps, the intake is excessive, at another time it is insufficient, but on the whole the general balance is maintained. The mean value for the calorific requirements of the body can be calculated from known data. For a healthy individual weighing 70 kilogrammes, engaged in the ordinary duties of life, 40 calories per kilogramme body-weight per diem, making 2,800 calories in all, are required (see discussion on Chittenden's experiments). The calorific supply may be made up as follows :

	Calories.
120 grammes protein	492
150 grammes fat	1,395
30 grammes alcohol	210
170 grammes carbohydrates	700
Total	2,797

It is reasonable to suppose that at certain times slight changes may occur in taste, or in choice of food, or in its preparation and quantity, whereby the calorific value of the food may be raised to slightly exceed the mean. On a diet, for example, containing a little more albumin, fat, and carbohydrate, the calorific value may be increased by 200 while the individual continues to engage in his usual duties. These 200 calories represent such a small amount of food that neither eyesight nor appetite afford any indication of it, and therefore the person can say to the best of his knowledge that his food-supply has not been altered, although he has obviously become corpulent. The 200 calories in question are contained in—

$\frac{1}{3}$ litre milk,
or 25 grammes butter,
,, 200 grammes lean meat,
,, 100 grammes fat meat,
,, 90 grammes rye-bread,
,, $\frac{4}{10}$ litre light beer.

Cases in actual life in which the mean calorific value of the food-supply is unknowingly exceeded occur very frequently, and the actual meaning of the small excess of 200 calories per diem may be illustrated by the following calculation : The entire food excess, with the exception of a small fraction negligible in this calculation, is laid up in the fat

depots, 200 calories corresponding to 21·5 grammes fat, so that a total fat accumulation of 7·85 kilogrammes may occur in one year. As the fatty tissues contain water, the increase in weight may be as much as 11 kilogrammes.

The example just cited is characteristic of what occurs very often in every-day life, and is intended to express numerically how, by an insignificant increase in the food over and above the amount actually required by the body, a state of obesity may gradually develop. It shows, further, how large the calorific value, and yet how small the actual amount of the food required may be in order to produce such a state.

There is no fundamental difference between this form of obesity and other forms in which a disproportion between the amount of food supplied and that utilized is brought about by a gradual though incomprehensible diminution in muscular activity. Such cases are quite as numerous, and these persons become obese as the result of insufficient physical exercise. This may be due to an inherent desire on the part of the person for ease, or to some infirmity, such as heart failure or disease of the limbs, or it may be the result of a phlegmatic temperament, whereby the individual leads a sedentary indoor life with little or no opportunity for engaging in active work. Such individuals become less healthy, but not through a diminished capacity on the part of the cells to carry on their oxidation processes. If the cells were permitted to work, then they would carry out their functions even as extravagantly as those of the normal individual. If the disinclination for muscular exercise is combined with an increased indulgence in food—which is, unfortunately, only too often the case—then the danger of undesirable corpulency is, naturally, doubled. There can be no doubt but that obesity so produced must be regarded as a disease, for the functions of the various organs of the body, in particular those of the vascular system, are damaged, and life may be thereby shortened. One cannot, however, regard this as disordered metabolism, for the metabolism of such obese persons is normal, and remains so ; it is the mode of living which is abnormal (exogenous obesity).

Clinical experience, as well as experimental results, show that this form of obesity is by far the most common. It is generally recognised as such, and the question only remains whether or not a form of obesity occurs which is the result of impaired energy exchange.

2. Obesity due to Retarded Metabolism—Endogenous Obesity.

It is the general opinion of both physician and layman that there are obese persons whose condition is to some extent independent of overeating or deficient physical exercise, and is rather the result of a "constitutional tendency." Such cases cannot be brought under control through intelligent regulation of diet and exercise. Expressed in the language of metabolism, this would denote that their corpulency was due to a slowing in the processes of metabolism, or, in other words, to an abnormal cellular activity inherited or acquired in after-life. The

abnormal condition may be advantageously expressed by the much misused phrase, "a slowing of metabolism." I mean thereby that the unit of protoplasm in such a case consumes less material in doing external work than in the normal individual.

The question can only be answered by a careful, and at present somewhat difficult, investigation. Several methods have been suggested.

(*a*) By determination of the oxygen consumed.

(*b*) By determination of the total daily exchange.

(*c*) By determination of that diet which will serve to maintain or to increase the body-weight when continued over a considerable period.

(*a*) *The Consumption in Oxygen.*

The first estimations of this kind were carried out by Zuntz and von Noorden (3). They were made in regard to the consumption of O_2 upon two obese persons at rest and during a state of fasting (see Vol. I., p. 198). Similar experiments have been made by Thiele and others (4).

The following table includes the whole of the existing records :

No.	*Sex.*	*Age.*	*Weight.*	*Height.*	*O_2 consumed in c.c. per Minute.*	*O_2 consumed in c.c. per Kg. per Minute.*	*Author.*
		Years.	Kg.	Cm.			
1	M.	30	94·0	167	256·1	2·71	Von Noorden
2	F.	35	70·0	Small	233·1	3·33	
3	F.	—	124·5	—	287·2	2·31	Thiele and Nehring Stüve
4	M.	35	97·0	—	272·0	2·80	
5	Child	4	48·8	129	153·6	3·15	Magnus-Levy
6	F.	64	69·5	151	239·8	3·45	
7	F.	56	76·0	144	188·6	2·48	
8	F.	25	77·0	156	226·6	2·94	
9	F.	57	88·0	?	330·2	3·74	
10	F.	43	107·0	160	257·3	2·40	
11	F.	32	111·4	160	257·3	2·40	
12	F.	41	133·3	152	282·0	2·12	
13	M.	23	80·2	174	257·8	3·22	
14	M.	43	80·1	169	278·6	3·48	
15	M.	71	91·5	169	258·0	2·82	
16	M.	28	92·7	167	262·2	2·83	
17	M.	46	96·0	167	231·2	2·41	
18	M.	48	109·0	167	307·2	2·82	
19	M.	28	126·0	163	414·0	3·29	Jaquet and Svenson
20	M.	53	112·0	173	357·0	3·17	
21	M.	46	90·0	165	268·0	2·97	
22	Same as 21	46	90·0	165	232·0	2·58	
23	F.	18	98·0	168	249·0	2·54	Salomon
24	F.	16	73·0	163	199·0	2·72	

Several of these "average" figures for the oxygen consumed are probably higher than the real values for such cases when at rest and in

the fasting state, for the patients were not sufficiently accustomed to the technique of the experiment to maintain a state of rest over a sufficiently long period. Nevertheless, if one considers this and deducts from all the above figures 10 per cent. for experimental error, they are still too high to admit of the conclusion that a diminished cellular activity exists in the obese state. Several of the values, not only absolute, but also relative to the height and the weight of the person, lie, it is true, below the lowest value for the normal. They are perhaps pathological, but we have no guarantee for this, and therefore they do not substantiate far-reaching conclusions. One ought not, however, to forget that the value for the oxygen consumed, when reduced to c.c. per kilogramme body-weight, must be less than the normal value. It is not for the entire body that the intensity of metabolism and consumption in oxygen is determined, but only for the total mass of living protoplasm, the inactive fat taking no part in the respiratory exchange. It is probable, however, that one could discern pathological deviations from the normal by reducing the values found to the superficial developments of the body. Unfortunately, this calculation cannot be made from the above figures, but in future experiments this must be considered. The various steps in such a calculation are given by Rubner (5).

The experimental study of the influence of exercise on the metabolism of vigorous and muscular persons of obese tendencies shows that they can accomplish a piece of work with the same expenditure of energy as a healthy person. Obese persons of weak constitution utilize less economically the calories set free—for example, the amount of work accomplished in climbing a stair only represented 11 per cent. of the calorific expenditure compared with 25 per cent. in the normal (see Vol. I.).

The work of Jaquet and Svenson appeared to suggest new ideas. They found no appreciable diminution in the metabolic activity of the obese during a state of rest or fasting. They examined later the increase in the oxygen consumption after food, and came to the conclusion " that the increase in the amount of oxygen used is appreciably less and of shorter duration in an obese subject than in the normal individual ; it is possible, indeed, to establish an evident tendency towards a sparing of material large enough, *ceteris paribus*, to account for a fat accumulation in the body." This would point to an actual diminution in the metabolic activity of the obese organism. In other words, obese persons would appear to accomplish the work of digestion with less calorific expenditure than the ordinary individual. The calculation made by Jaquet and Svenson is, however, faulty and inadmissible. They calculate the percentage increase in the oxygen consumption on the fasting period brought about by the work of digestion, and find that this increase is less than was found by A. Magnus-Levy for normal cases. In their calculation, however, two quantities are brought together which are not in reality comparable—the energy consumed during a state of rest and the work during digestion. If the body-weight is not approximately that of the average, then one can only strictly compare the absolute increase in energy expenditure which alone affords an estimate of the work of digestion in healthy and in corpulent persons. By doing so

we arrive at values for the obese which are almost identical with the normal.[1]

Reach (6) found in one case (a boy of fifteen years, weighing 63 kilogrammes) that 19 c.c. more oxygen was consumed in the third hour after dinner, and 41 c.c. in the fifth hour, than the normal amount for a condition of rest and fast (208·9 c.c.). The first value is less than any hitherto found, but the second is normal.

The evidence at our disposal renders it in the highest degree probable that many obese persons accomplish work, and in particular the work of digestion, with less expenditure in energy than the normal individual. I have already pointed out the possibility of this, but to pass from the probable to the certain there is still another step. The experiments of Jacquet and Svenson and Reach cannot so far be regarded as affording sufficient and reliable evidence of diminished energy expenditure in obese cases. A far more thorough investigation must first be made, and the critical discussion of this subject by Magnus-Levy (Vol. I.) shows how difficult it is to draw decisive conclusions.

[1] The tables given by Jaquet and Svenson may be here reviewed:

Value of O_2 in c.c. during Period of Rest.	*Absolute Increase in the Amount of O_2 consumed per Kg. and Minute.*										
	After Breakfast.			After Dinner.							
	First Hour.	Second Hour.	Third Hour.	First Hour.	Second Hour.	Third Hour.	Fourth Hour.	Fifth Hour.	Sixth Hour.	
338	+70	—	+11	—	+93	—	+89	—	+7	Case L. K.
322	+59	—	+11	+79	—	+49	—	+34	—	
339	+41	—	+14	+72	—	+48	—	+4	—	
Mean	+57	—	+12	+81		+62		+15		
268	—	+33	—	—	+47	—	+40	—	—	Case K. Z.
268	—	+72	—	—	+50	—	+20	—	—	
Mean	—	+52	—	—	+49	—	+30	—	—	
217	+58	+58	+35	+87	+76	+58	+41	+36	+19	Magnus-Levy (7); mean of three determinations.
Normal				+82		+50		+27		

The variations from the mean normal value here found are sometimes negative, sometimes positive. They are too small to admit of far-reaching conclusions. This is still more evident when one compares the individual figures found by Magnus-Levy, from which the mean values are calculated. Even in the healthy individual variations occur greater than those which Jaquet and Svenson deem pathological (compare Magnus-Levy, Vol. I., p. 343).

(*b*) *The Total Daily Exchange.*

Under this heading only one well-conducted and complete series of experiments is on record [Rubner (5)]. The investigator compared the total daily exchange in the case of two boys by determining their total consumption in food and their total outputs, inclusive of CO_2. One boy was eleven years of age, weighed 25·65 kilogrammes, his height being 135 centimetres; the other was ten years, weighed 40·59 kilogrammes, and measured 136 centimetres. They were brothers brought up in exactly the same surroundings, so that there was very good reason to suppose that the younger boy was a typical case of endogenous obesity.

Rubner found that the obese child did not give the slightest indication of what he could term diminished vital energy; his energy exchange was even greater than that of his lean brother, and corresponded to that of a normal individual of the same weight.

	Calories from—			*Total.*	*Author.*
	Protein.	Fat.	Carbohydrate.		
Lean boy (25·6 kilogrammes) ..	225	655	635	1,515	M. Rubner.
Fat boy (40·6 kilogrammes) ..	230	828	779	1,817	
Boy (24 kilogrammes), healthy ..	271	355	963	1,584	W. Camerer (8).
Boy (40 kilogrammes), healthy ..	328	428	1,148	1,904	

By reducing the values to the kilogramme body-weight, differences, of course, were found. The heat production in the lean boy amounted to 52·0, and in the fat to 43·6 calories per day and kilogramme. Rubner then calculated from the specific gravity of the two boys (specific gravity of the lean = 1038, of the fat 975) how much more fat the one had than the other. If now, after deducting the weight of this excess fat from the weight of the obese boy, the energy exchange had been the same for both boys, then one should have found the value 35 calories per kilogramme for the fat one; 43·6 calories was the value actually found.[1] The body mass remaining after deduction of the excess fat had, therefore, an activity in metabolism considerably greater than that of the normal.

The values here found agree fairly closely when determined with respect to the superficial developments of the two boys: for 1 square metre surface there was an energy exchange by the lean boy of 1,290 calories, by the fat boy of 1,321 calories. On another occasion Rubner found that for 1 square metre of surface 316·08 grammes CO_2 were produced in twenty-four hours by a lean man weighing 58 kilogrammes, and 325·20 grammes CO_2 by a man of obese tendencies weighing 101 kilogrammes. Here also the tissue mass remaining after deduction of the excess fat was apparently more active than that of the leaner individual.

[1] For the method of calculation, see the original paper (5).

The experiments of Rubner are the most accurate which we possess. They show that it is possible for a condition of extreme obesity to develop although the protoplasmic energy of decomposition is supernormal. It stands to reason, however, that one cannot generalize from these few figures. The observations must be extended to a number of obese cases, in particular to such as have been clinically diagnosed, with due consideration of all existing outside circumstances, as endogenous in origin. Unfortunately the experiments are tedious, and require a great deal of time for their execution.

(*c*) *Food.*

A determination such as this has the advantage in that it can be applied to a very great number of cases. It requires, however, a special knowledge and acumen on the part of the observer in order to make such a method reliable. From the following cases, however, it would appear certain that weight was maintained, or even increased, although the calorific value of the food was cut down to less than that of the customary or required value for such individuals.

Von Noorden (9) : A man, aged thirty-nine, weight 102 kilogrammes, exercised freely in the open air. For three months he was kept on a diet the calorific value of which never exceeded 1,720 calories. After the expiry of the three months he weighed 101 kilogrammes. Had his energy exchange been normal, then his calorific requirements might reasonably have been estimated 1,000 calories higher, or his weight, under the conditions to which he was subjected, should have fallen considerably. Indeed, in another case (that of a man kept on the same regulation diet, but much less actively engaged) the weight fell from 98 to 93·2 kilogrammes in four weeks.

Von Noorden (9) : A married woman, aged sixty-five, weighing 86 kilogrammes, gained 0·5 kilogramme in six weeks on a diet equivalent at most to 900 or 1,000 calories. She certainly took but little exercise, but under normal conditions of metabolic activity she ought to have lost weight considerably.

Schwenkenbecher (10) reports clinical observations on two obese girls. One of these first began to show signs of losing weight when the value of the food material was reduced to 17 calories per kilogramme. She was kept in complete confinement and in bed. The absolute value in calories of the food consumed amounted to 1,020 (Marie S., nineteen years) and 1,105 (Sophie W., seventeen years).

Salomon (4) : An obese girl, sixteen years of age, weighing 71·4 kilogrammes, increased in weight ½ kilogramme in eight days on a regulation diet equivalent to 1,300 calories. She had plenty of open-air exercise, and was under the strictest supervision in my own hospital. By maintaining the calorific value at about 1,900, the weight remained constant for some months afterwards. The girl had not only an excessive accumulation of fat, but was muscularly well developed and energetic in her movements.

All these cases, discussed here as carefully as possible, show that a determination of the exchange according to Rubner's method would in all probability have led to other results than those which he found for his obese boy. The collection of further material is very necessary, and in the meantime the question as to whether cases of obesity occur as the result of diminished protoplasmic activity can only be affirmed with a certain amount of reserve.

At all events, it is certain that cases occur far more frequently than the layman or many physicians from mere superficial observations are aware of.

3. Influences bearing on the Energy Exchange.

(*a*) *Administration of Preparations of the Thyroid Gland.*

Yorke-Davies (13) and Wendelstadt (14), working independently of each other, observed the effect of thyroid substance on the weight of obese patients. The communications of Leichtenstern (15), which were really based on the observations of Wendelstadt, brought a short wave of popularity for the treatment of corpulency by thyroid preparations. Later it was shown in my own hospital by my assistant at the time [Magnus-Levy (16)] that the therapeutic action of preparations of the thyroid gland in reducing corpulency was due to stimulation of the metabolic processes (increased consumption of oxygen and output of CO_2). This has since been confirmed by numerous experiments, aud in particular by another thorough series of investigations by Magnns-Levy (4). I shall content myself, therefore, with an indication only of the fundamental facts. Their biological significance and the individual points have been already thoroughly discussed in another part of this work (see chapter on the Thyroid Gland). For the clinical and the therapeutical reasons for the speedy abandonment of the thyroid method of treatment, consult my original paper on Obesity (2).

(*b*) *Castration.*

It is the opinion of clinicians in general that castrated men, and women on whom ovariotomy has been performed, show a tendency towards obesity. For many centuries such cases have been brought forward as typical examples of corpulency of constitutional origin due to diminished metabolic activity. Loewy and Richter (17) were the first to take up the experimental side of the question, and they investigated the respiratory gas exchange in dogs, as well as in bitches, before and after castration. The amount of O_2 consumed per kilogramme body-weight fell 20 per cent. in the case of bitches, and about 14 per cent. and more rapidly in the case of dogs after castration. Expressed in absolute value (namely, not reduced to the kilogramme body-weight), the total gas exchange in bitches after removal of the ovaries fell about 12 per cent. In a later communication from A. Loewy (18) on this subject, the same reduction on the original value was stated to exist

after two and a half years. After that time a further diminution occurred.

If this experimental teaching be applied to the human being—as it indeed may—we have a glowing illustration of the occurrence of endogenous obesity and a satisfactory explanation for the above-mentioned clinical teaching in regard to castration.

Lüthje (19), who has likewise studied the question, finds results which are not in accordance with those of the above-mentioned workers. He found, for example, no difference in the energy exchange between castrated and non-castrated bitches. As Loewy and Richter (20), however, point out, Lüthje's experiments are not conclusive, and do not contradict the results which they obtained in their work (see Vol. I.).

(c) *Restriction in the Amount of Water.*

Since the appearance of the articles by Oertel and Schweninger on the treatment of obesity, the idea has become universal with laymen and physicians alike, that restriction in the use of water favours the reduction of fat, and that this reducing effect is the result of an increased activity of metabolism of the fat irrespective of the total metabolism (21). The fact can no longer be disputed that a moderate restriction in the use of fluid is beneficial in some cases of corpulency, but in others it is absolutely useless. Clinical teaching alone has shown that the effect produced by restricting the use of fluid is not the result of any influence which this restriction brings to bear on the metabolism of fat, but depends on other causes which, although of great interest from the clinical side, do not affect the question of the metabolism of the obese [von Noorden, Rosenfeld, Salomon (22)].

After Landauer and Straub had succeeded in showing that the adipose fat in healthy animals was not diminished by restriction in the amount of water consumed, Salomon confirmed the observations of Landauer and Straub for obese persons (4, 23, 24).

The determination of the respiratory gas exchange gave :

	Oxygen Consumed per Minute[1]—		
	Before Thirst.	Period of Thirst.	After Thirst.
	c.c.	c.c.	c.c.
In chlorosis	221·8	206·6	204·3
	242·3	233·5	234·7
	217·5	205·6	202·6
In anæmia	209·4	196·6	202·7
In nephritis	203·7	196·5	202·9
In obesity	262·5	249·5	—
	214·1	198·9	199·1

[1] Average figures for period of rest.

Hence it would appear that a condition of thirst exerts no influence at all on the energy exchange. These experiments, at all events, point to a diminution rather than to an increase in the respiratory exchange. The interpretation attached to the clinically interesting and important discovery of Oertel and Schweninger can no longer hold good. Nor is such an interpretation necessary, since the secondary effects of a condition of thirst—influence on the desire for solid food and on the circulatory system—are more than sufficient in themselves to explain the results obtained (22).

II.—THE METABOLISM OF PROTEIN.

Since the classical researches of the school of Voit first showed that the adipose depots of the body, as well as the fats contained in our foods, tend towards economy of protein, the question of maintaining protein equilibrium in obese cases on an ordinary but plentiful diet has never been raised. Whether or not this law of protein economy—true, undoubtedly, for the shorter periods during which determinations on metabolism are made—is also valid throughout for chronic cases of obesity is still a subject for discussion. Here the protein of the body is not alone dependent on the nature of the food, but on the working conditions of the tissues rich in protein, especially muscular tissues. When these are not exercised, and become embedded in fat, then the body becomes muscularly weak, and will, with time, continue to give up protein in spite of adequate nourishment. Experimental proof of this is still wanting, and is not likely to be undertaken, the investigations necessary thereto being too laborious.

A more interesting question is that of the protein metabolism during the treatment of obesity. Its solution is the more necessary because of the numerous discussions in regard to the most suitable form of diet in the treatment of obesity. The discussion between Oertel and Ebstein (25) in the middle of the eighties aimed at the solution of the problem on theoretical grounds. Moreover, it was taught by Hirschfeld, Klemperer, and others (26) that increase in protein was to be expected from over-nourishment and a loss from under-nutrition, and in this latter hypothesis lay the treatment of obesity.

The theoretical discussions, protracted and wearisome, have been brought to a satisfactory conclusion. Von Noorden and Dapper (27) have shown that it is possible to reduce the calorific value of the food-supply to one-half that of the calculated requirements in the case of obese persons, and by this means to obtain a loss in weight without any material increase in the nitrogen output. In this, then, lies a difference between the obese and the normal individual, or the man with but a meagre fat-supply. Fat accumulation in obese cases tends to suppress to some extent the unfavourable effects which under-nutrition in the normal individual produces on the protein of the body. Of course, this protective action is only exerted within certain limits, but the extent

to which the calorific value of the food-supply is limited in the successful treatment of obesity by such means does not necessarily exceed these limits.

The opposing results obtained by Hirschfeld (28) may be accounted for by a too vigorous reduction in the amount of protein, as well as in the calorific value of the food [Dapper (29)]. Numerous recent investigations, in which the calorific as well as the protein value of the food-supply was varied in many ways, all tend to confirm the results of von Noorden and Dapper (30). In these cases nitrogenous equilibrium was obtained—at least, when the restriction in food was not too severe—and, indeed, in some cases a slight addition in nitrogen was observed during the treatment of obesity by this means. In order to ensure the best results, gradually increasing muscular exercise, combined with restriction in the number of calories consumed, is advisable. In this way the conditions conducive to the accumulation of protein are considerably improved (see Vol. I.).

In this connection may be cited a careful experiment by Hellesen (31) on the metabolism of an obese girl of 12 years. Hellesen found that it was possible to maintain nitrogenous equilibrium when the diet was only one-fifth to two-fifths of that necessary for the patient's normal condition, and that the best results were attained when the fat rather than the carbohydrate portion of the food was cut down. On further reduction in the calorific supply, he found, however, a marked loss in nitrogen. This is in complete harmony with the clinical observation that children, when put on a very low diet, often become for a considerable period quite perceptibly reduced in strength.

The use of thyroid preparations in obesity produces results different from those which accompany the usual methods of treatment in that it is usually accompanied by great loss of nitrogen (32) (see Thyroid Gland). This is one reason why the thyroid treatment has been discarded. An excessive restriction in fluid is similarly dangerous [Salomon (4)].

III.—THE DIGESTIVE ORGANS.

Clinical teaching has shown that dyspeptic disturbances of various kinds occur in cases of obesity. The most prominent of these is constipation and its consequences. Attention is merely drawn to this, as well as to the hæmorrhoidal troubles associated with obesity.

1. The Appetite.

In the milder degrees of obesity the appetite is usually good. The close physiological relationship between the actual amount of nourishment required by the tissues and the amount of food desired by the appetite appears to exist no longer; immoderate eating and the further

accumulation of fat are the results. In the advanced stages of obesity the appetite is often diminished. Nevertheless, though the actual amount of food taken is small, the obese condition may be maintained, or even increased. Such persons are usually weak, and are subject to every form of ailment ascribed to this particular form of obesity known clinically as "anæmic obesity." This form, however, does not warrant any special description from the standpoint of metabolism. The increase in fat, in spite of a diminished food-supply, is fully explained by the resting condition of the muscles, to which the weakness in certain cases is due.

2. Secretion by the Stomach.

No special work appears to have been done in regard to the digestive processes occurring in the stomach in cases of obesity. I have often had the opportunity, however, of washing out the stomach in such cases, and found in general that the production of hydrochloric acid, as well as the rate of discharge from the stomach, was normal even in cases where stomachic troubles of the general type were described. On the other hand, in many cases there was a diminished HCl production and an abundant secretion of mucus, while less frequently cases of hyperacidity occurred. Out of 19 cases of obesity in which the stomach contents were examined on account of various dyspeptic troubles, 10 showed a normal production of hydrochloric acid, in 6 there was hypo- or anacidity, and only 3 exhibited hyperacidity. All these disturbances are to be regarded as accidental complications, and are of more clinical than purely pathological interest [von Noorden (33)].

Nothing is known regarding the secretion of bile and of pancreatic juice. On the influence upon digestions of complications associated with diseases of the pancreas, see Vol. II., Chapter IV.

3. Absorption of Food.

Our practical knowledge regarding the absorption of food in cases of obesity has been acquired incidentally through investigations in regard to the metabolism of protein. It was found that the absorption, with regard to the most important factors—viz., dry substance, nitrogen, and fat—was quite normal, so that I may refrain here from quoting the actual figures (34). Only in one case [Rubner (5)] was the absorption of nitrogen impaired. In the daily consumption of 9 grammes nitrogen (59·9 grammes protein) there was a loss of 1·88 grammes (20·91 per cent.). This isolated case Rubner has rightly described as due to accidental digestive derangement rather than to a condition peculiar to the metabolism of the obese.

IV.—THE BLOOD.

1. Quantity.

In advanced cases of obesity there would appear to be a relatively abnormal deficiency of blood—*i.e.*, the blood quantity is reduced in comparison with the weight of the body. Only 2·25 per cent. of blood was found in fattened pigs, compared with 7·8 per cent. in the normal [Heissler (35)]. For man there are no statistics on record.

2. Concentration.

The concentration of the blood does not often undergo any appreciable change. Bouchard found on the average about five million blood-corpuscles in the blood from obese persons.

In cases where the muscular strength is maintained, and where the clinician speaks of "plethoric obesity," the density of the blood frequently appears to be increased. Kisch (37) found in seventy-nine out of one hundred cases of obesity that the hæmoglobin of the blood was normal or slightly increased (to as much as 120 per cent. of the normal). He employed Fleischl's method, which is, however, not very reliable. In 21 per cent. of the cases the hæmoglobin was diminished, but syphilis, the misuse of alcohol, and menstrual derangements played a predisposing part in these instances. Oertel (38) has also found that in cases of obesity in which the power of the heart was not impaired, or where there was no indication otherwise of a deranged circulation, the hæmoglobin was often increased to about 5 to 8 per cent. above the mean normal value. In five cases of muscular but excessively obese men, Poll made blood-counts, and found 5·2 to 5·8 millions erythrocytes. In another two obese cases I observed 7·2 and 7·7 millions red corpuscles. The patients weighed 115 and 105 kilogrammes respectively.

Many obese persons suffer, on the other hand, from anæmia. Their outward appearance indicates this, and an examination of the blood confirms it. On this account a specific form, "anæmic obesity," has been spoken of. This is justifiable from the clinical side as of prognostic, as well as therapeutic value (39). The anæmia is to be regarded, however, only as a complication, and not as a derangement in the metabolism closely connected with the obese condition. Kisch found that the hæmoglobin was diminished in 21 per cent. of his cases of obesity. Leichtenstern (40) determined the extinction coefficient in four cases, and found the values 1·106, 1·187, 1·191, and 1·075, compared with 1·298, the mean value for healthy persons under similar conditions. In the advanced stages of obesity, accompanied by cardiac failure and dropsy, the hæmoglobin may fall to one-half of the normal [Kisch]. We found in five cases of marked obesity in women with anæmia but no œdema that the decrease in the hæmoglobin amounted to between 60 to 70 per cent. of the normal value (Gower's hæmoglobinometer).

Observations upon the condition of the blood of obese patients during a course of treatment are of value. Grawitz carried out at my request such a series of investigations on two patients whose metabolism was being determined by Dapper (41).

K., aged fifty-one, female. Weight before commencing treatment 78·85 kilogrammes; food intake, 14 to 15 grammes nitrogen daily. The calorific value at first was 1,470 to 1,500 calories; it was gradually cut down to 1,120. Nitrogenous equilibrium was maintained throughout the entire period. During the thirty-two days on which the experiments were carried out the weight of the patient fell gradually to 73·1 kilogrammes.

Day.	*Dry Substance in the Blood.*	*Dry Substance in the Serum.*
	Per Cent.	Per Cent.
2	21·49	9·77
6	20·34	10·59
18	19·69	9·90
24	20·04	8·84
30	20·35	?
32	19·29	9·20

E. S., aged forty-four, female. Weight before the commencement of the treatment, 80·9 kilogrammes; food intake, 14 to 15 grammes nitrogen. At the commencement of treatment the calorific value of the food lay between 1,480 and 1,500, and it was gradually reduced to 920 calories. Nitrogenous equilibrium was maintained, or there was a slight increase in the retained nitrogen, with the exception of the last eight days, when the calories were reduced to less than 1,000. The final weight after the forty days during which determinations were made was 74·3 kilogrammes.

Day.	*Dry Substance in the Blood.*	*Dry Substance in the Serum.*
	Per Cent.	Per Cent.
2	21·10	9·50
6	22·85	9·76
18	21·82	9·35
24	22·00	9·58
32	20·82	9·97
44	20·29	8·64

In both the patients there was a slight falling-off in blood concentration during treatment. Corpuscles as well as serum show this. Particularly striking is the drop towards the close of the second experiment, where the calorific value of the food was cut down more than usual and nitrogenous equilibrium could no longer be maintained.

Denning describes a case which throws light on the effect produced by thirst in cases of obesity (42). A young man, aged twenty-three, weighing 93 kilogrammes, took 635 c.c. liquid daily for six successive days. The specific gravity of his blood before commencement was 1028·5; at the

end of the period of thirst it had risen to 1031·8. He lost 4 kilogrammes in weight during this time, but only through loss of water from his body. There was no reduction in the amount of fat, the calorific value of the food being too high for this (2,900 calories).

3. Alkalinity.

Burmin determined the alkalinity of the blood by Landois' method in two obese cases, and found that it was diminished. He took as normal 182 to 218 milligrammes NaOH in 100 c.c. blood, and found 164 milligrammes in the one obese case (144 kilogrammes) and 164 milligrammes in the other (104 kilogrammes); the hæmoglobin and blood-corpuscles were normal (43). Compare the observations of Magnus-Levy in Vol. I., p. 179.

4. The Fat in Blood.

It would appear that the blood of obese persons has been found on several occasions to contain an increased amount of fat. Kisch (37) states that the mean value of 0·2 to 0·3 for the fat in blood increases in cases of excessive obesity to double or treble this amount. Cantani (44) also states that lipæmia occurs frequently in advanced cases of obesity, but no special data relative to the amount of this fat in blood are given by him. I have often investigated the condition of the blood in the most marked cases of obesity, but have never met with the characteristic milky appearance of the serum. Further observations are necessary. In these, attention should be paid to the time as well as to the nature of the last meal, for at the height of fat digestion the fat in the serum under normal conditions may increase to more than 1 per cent.

V.—THE URINE.

1. Quantity.

The quantity of urine in obese cases where complications are absent is usually normal or slightly subnormal. Kisch (37) found, for example, as an average for twenty-five obese cases, the value 1,450 c.c. per diem. I found in ten cases of very obese men an average of 1,250 to 1,550 c.c., and in twelve cases of obese women an average of 1,080 to 1,350 c.c. daily. There was no restriction on the amount of liquids taken. When the amount of urine remains below normal, the explanation is usually to be found in a vigorous excretion of sweat to which the obese are particularly prone. In other cases, complications involving kidney and heart troubles are concerned. Apart, however, from these diseased conditions, which have nothing to do with the disturbed metabolism in obese cases generally, the quantity of urine is frequently controlled by therapeutic agents. The most important is a restriction in the amount of fluid, which is

observed by most obese persons even without the express command of the physician.

A restriction in the amount of fluid taken leads naturally in the case of healthy persons to a reduction in the volume of the urine, and as Oertel (38) has shown, this reduction is the same in obese cases where the circulatory and secretory organs are healthy. The fall in the quantity of urine excreted is almost proportional—within certain limits—to the reduction in the amount of fluid taken, so that the urine represents about 68 to 80 per cent. of the total quantity of liquid consumed.

When, however, heart failure, dropsy, or hydræmia is present, the amount of urine excreted in obese cases, just as in cardiac dropsy, may not always diminish in the same ratio as the fluid consumed is reduced, but frequently remains constant, or indeed increases. In this way the withdrawal of water from the body is brought about, so that the circulation may be considerably improved. Striking examples are to be found in Oertel's work, but a case which I have myself observed may be quoted here.

A patient, aged fifty-two, weighed 125 kilogrammes two months prior to observation. Then, as the result of overexertion, heart failure and œdema of the lower extremities developed, and the weight increased gradually to 142 kilogrammes. The treatment during the period shown below consisted solely in the gradual reduction in the amount of liquid taken. The amount of solid food was not reduced, but in view of the weak state of the heart further treatment had to be postponed.

Days on which Observations were made.	*Mean Liquid Taken.*	*Mean Quantity of Urine.*	*Notes.*
	c.c.	c.c.	
1–3	2,550	950	At the commencement the amount of fluid taken was at the option of the patient. Initial weight 142 kilogrammes; final weight 123 kilogrammes.
4–6	2,000	960	
7–9	1,500	1,050	
10–12	1,000	1,480	
13–18	800	1,900	

2. Substances containing Nitrogen.

(*a*) *Total Nitrogen.*

See the Metabolism of Protein, p. 703.

(*b*) *The Several Nitrogenous Compounds.*

Normal values were found both by Leven (45), in his determinations of the ratio of the total nitrogen to the urea nitrogen in obese cases, and by Setti (46), who determined the other nitrogenous constituents of the

urine as well. Setti's patient was forty years of age, and weighed 103 kilogrammes. The analysis of the urine on three consecutive days gave the following results :

	First Day.	*Second Day.*	*Third Day.*
Total nitrogen	21·07 grammes	24·75 grammes	21·92 grammes
Urea nitrogen	86·76 per cent.	87·18 per cent.	87·62 per cent.
NH_3 nitrogen	3·86 ,, ,,	3·72 ,, ,,	4·05 ,, ,,
Uric acid nitrogen ..	1·20 ,, ,,	1·11 ,, ,,	1·07 ,, ,,
Residual nitrogen ..	8·18 ,, ,,	7·99 ,, ,,	7·26 ,, ,,

The estimations which I made, and have already published in the first edition of this work, also gave normal values : Urea nitrogen 85 to 88 per cent., ammonia nitrogen 3 to 6 per cent., uric acid nitrogen 1 to 2 per cent. of the total nitrogen.

(*c*) *Uric Acid.*

The older values, determined without considering and allowing for the purin bodies introduced in diet, were normal [0·6 to 0·8 gramme uric acid, von Noorden (2)]. I had a series of uric acid determinations carried out in connection with three obese patients under mild treatment. They were kept at the commencement on a diet free from purin bodies, and after some days each patient received, in addition to his ordinary food, an additional 400 grammes of meat (weighed raw).

Day.	*Food.*	*Patient* 1 (106 *Kg.*).	*Patient* 2 (112 *Kg.*).	*Patient* 3 (126 *Kg.*).
1, 2, 3, 4	Purin-free	Gm. 0·409	Gm. 0·510	Gm. 0·389
5	+ 400 grammes meat	0·681	0·800	0·572
6	+ 400 grammes meat	0·720	0·803	0·791
7	Purin-free	0·479	0·522	0·500
8	Purin-free	0·411	0·527	0·376

None of these patients showed complications of any sort, and the values obtained were quite normal.

(*d*) *Albuminuria.*

Albuminuria occurs frequently in the more marked degrees of obesity, but more particularly in cases of long standing. Circulatory disturbances and diseases of the kidney are its most probable causes. Albuminuria, however, is not connected with the metabolism of the obese. Bouchard (36) found albuminuria in 26 per cent. of his cases, and my own statistics yielded similar results—namely, 27·6 per cent. [von Noorden (2)].

3. The Nitrogen-free Constituents of the Urine.

(*a*) *Oxalic Acid.*

Crystals of calcium oxalate have frequently been found in the urine obtained from obese cases, and not infrequently in large quantity (47). The conclusion drawn from this—viz., that the oxalic acid is increased in obese cases—and the further hypothesis which attributes its increase to impaired powers of oxidation, cannot hold good, as the determination of oxalic acid from the quantity of sediment can obviously lead to erroneous conclusions. Quantitative determinations of the oxalic acid have been made by Kisch (48), but unfortunately without sufficient regard to the quantity of urine and the nature of the diet. In nine cases of advanced obesity of the ordinary type Kisch found per litre of urine, 18·0, 11·0, 11·3, 11·7, 5·4, 40·0, 4·9, 7·5, 5·8 milligrammes oxalic acid; in another four cases 5·8, 11·7, 11·3, 6·3 milligrammes. Only one figure (40 milligrammes) is very much above the normal, and this may be accidental, due, perhaps, to the diet, the composition of which is not stated.

(*b*) *Acetone.*

I have previously stated that obese persons do not exhibit acetonuria, even when their intake of food is lowered (under-nutrition) (49). This has been confirmed. Obese cases kept for some time on 50 to 60 grammes carbohydrate for the purpose of treatment, and living otherwise upon a diet of protein and fat, excreted no more than the ordinary traces of acetone. Here the body had become so accustomed to a diet rich in ketone-forming substances that an "antiketonic" habit was established. When, however, obese cases are fed on a diet rich in carbohydrates, and are suddenly deprived of this, the acetone increases just as it does in healthy persons [in one case to 2 decigrammes, and in another to 3·1 decigrammes on the third day, Mohr (50)].

(*c*) *Sugar.*

It is a well-known fact that glycosuria is frequently associated with obesity (51). Among every hundred diabetics Frerichs found 15 obese individuals, Seegen 30, Bouchard 45, and von Noorden 21. Kisch states that he has seen diabetes develop in more than half of his cases of "hereditary" lipomatosis, and in 15 per cent. of the "acquired" forms of obesity. For a certain number of cases, as I have already pointed out, the question whether the diabetic condition is not the primary one, and the obese the secondary one, must still remain open ("diabetogenous obesity").

We have to treat here of the occasional occurrence of glycosuria in cases of obesity. Fleiner and Hirschfeld (52) hold that the occasional occurrence of sugar is not uncommon, and attribute it to excessive food, with deficient muscular exercise. No great significance would appear to be attached to its presence. If the question, however, of the harmless-

ness of the occasional occurrence of sugar in obese cases is not to be disputed, I should at least like to give warning against such optimism, for I have only too often seen a regular diabetic condition develop after several years of such predisposition. I regard it, similarly, as an unfavourable symptom if the moderate addition of glucose (100 grammes) in obese cases produces alimentary glycosuria, for this does not occur in the majority of cases. Of fifteen obese cases in which I found sugar in the urine after 100 grammes glucose, five developed genuine diabetes later [von Noorden (53)]. It is true, of course, that the question of muscular exercise comes more into account in the glycosuria of the obese than otherwise in diabetes. An example may be cited. An obese diabetic excreted an average of 25·1 grammes of sugar daily during three days of rest, and none at all on two days when, although on quite the same diet, he took a considerable amount of walking exercise.

Individual communications regarding the frequency of alimentary glycosuria in cases of obesity yield little indicative information. Systematic investigation on broader and more uniform lines is desirable; it would explain what prognostic significance can be attached to the occurrence of alimentary glycosuria in obese cases, and would yield a valuable and ready indication for the prophylactic measures in the treatment of obesity.

VI.—THE INFLUENCE OF OBESITY ON THE ACTIVITY OF THE EPITHELIAL STRUCTURES.

1. The Excretion of Water.

Although it has been found impossible experimentally to establish differences between the heat production of the obese and that of the healthy individual, nevertheless certain characteristics distinguish the heat radiation of the obese from that of the normal individual. The investigations of Rubner and his colleagues show that the moisture given up by the skin at low temperatures and in dry air in cases of obesity is the same in amount as that excreted by lean persons under similar conditions (54). It is not appreciably increased by moderate energy expenditure in a dry atmosphere, and only slightly in a moist atmosphere.

The amount of water excreted hourly when the atmospheric temperature lay between 20° and 22° C. was—

60 grammes by a lean man (58 kilogrammes) in a dry atmosphere, and during a condition of rest.
56 grammes by a fat man (101 kilogrammes) in a dry atmosphere, and during a condition of rest.
60 grammes by a lean man in a dry atmosphere, with moderate exercise.
80 grammes by a fat man in a dry atmosphere, with moderate exercise.
25 grammes by a lean man in a moist atmosphere, and at rest.
27 grammes by a fat man in a moist atmosphere, and at rest.
50 grammes by a lean man in a moist atmosphere, with moderate exercise.
78 grammes by a fat man in a moist atmosphere, with moderate exercise.

Schwenkenbecher (10) obtained similar results by comparing the values obtained for obese and for lean children.

By higher temperatures, however, and especially during humid conditions of the atmosphere and muscular exercise, the amount of water given up through the skin in obese cases greatly exceeds that of the normal. The temperature limit of 28° to 30° C. forms the transition-point in the process of heat regulation in the case of obese persons.

Temperature.	*Amount of Water given up per Hour by a Lean Person.*		*Temperature.*	*Amount of Water given up per Hour by an Obese Person.*	
	At Rest.	During Work.		At Rest.	During Work.
	Gm.	Gm.		Gm.	Gm.
30°	100	145	28°–30°	134	169
35°	160	170	36°–37°	**217**	**357**
30°	65	110	28°–30°	**201**	**178**
35°	—	—	36°–37°	**441**	**535**

Of the 535 grammes of water excreted in the last experiment, 269 grammes disappeared by evaporation and 266 grammes as sweat.[1] In the experiments whose results are printed in bold type, an increase in the temperature of the blood occurred simultaneously (0·9° to 2·3° C.). The limits within which the obese can accommodate themselves in their heat radiation are therefore narrow, and under favourable conditions a considerable accumulation of heat energy may occur (during high atmospheric temperature and a humid condition of the air, and during muscular exercise). The secretion of water, which favours heat radiation, may increase to such an extent as to become troublesome. It has been determined that from 3 to 4 litres of water have been given off by corpulent persons under suitable conditions within a few hours. These experimental evidences stand in complete harmony with the facts of clinical observation.

2. The Secretion of Fat.

Leubuscher (56) is the only one who has studied the excretion of fat via the sebaceous glands. He states that corpulent individuals excrete less rather than more fat in this way. This confirms an incidental observation made by Krukenberg. More exact data are wanting.

[1] During profuse perspiration in obese cases considerable quantities of nitrogen may escape in sweat from the body. Cramer (55) calculated that as much as 1·88 grammes disappeared daily during vigorous exercise. This represented 12 per cent. of the nitrogen in the urine and fæces. Dapper (55) also found that the urinary nitrogen was reduced about 1 to 1·5 grammes on the days when a vigorous excretion of sweat took place, probably because the nitrogen-containing products of metabolism were being carried off in the perspiration.

LITERATURE.

1. Pflüger: Die Ernährung mit Kohlenhydraten und Fleisch oder auch mit Kohlenhydraten allein. Ar. P. M. **52.** 239. 1892.

2. v. Noorden: Die Fettsucht (in Nothnagel's spez. Path. u. Ther.). 1900.

3. v. Noorden: Path. des Stoffwech. P. 448. 1893.

4. Thiele u. Nehring: Untersuch. des respirat. Gaswech. unter dem Einfl. von Thyreoidea-Präparaten, etc. Z. M. **30.** 41. 1896.—Stüve: Über den respirat. Gaswech. A. K. (Festschr.). P. 44. 1896.—Magnus-Levy: Untersuch. zur Schilddrüsenfrage. Z. M. **33.** 269. 1897.—Jaquet u. Svenson: Zur Kennt. des Stoffw. fettsüchtiger Individuen. Ibid. **41.** 375. 1900.—Salomon: Ueber Durstkuren. N. k. A. H. 6. 1905.

5. Rubner: Beitr. zur Ernährung im Knabenalter mit besonderer Berücksichtigung der Fettsucht. 1902.

6. Reach: Stoffwechseluntersuch. an einem fettleibigen Knaben. Salkowski-Festschr. P. 319. 1904.

7. Magnus-Levy: Ueber die Grösse des respirat. Gaswech. unter dem Einfl. der Nahrungsaufnahme. Ar. P. M. **55.** 1. 1893.

8. Camerer: Der Stoffwech. des Kindes. **1894.**

9. v. Noorden: Nr. 2. Pp. 30, 32.

10. Schwenkenbecher: Ueber die Ausscheid. des Wassers durch die Haut. D. Ar. M. **79.** 29. 1904.

11. Stadelmann: Ueber Entfettungskuren. B. k. W. **1901.** Nr. 25.

12. Rubner: Nr. 5. P. 31.

13. Yorke-Davies: Thyroid Tabloids in Obesity. B. M. J. **1894.** 7 July.

14. Wendelstadt: Ueber Entfettungskuren mit Schilddrüsenfütterung. D. m. W. **1894.** Nr. 50.

15. Leichtenstern: Ueber Myxödem und über Entfettungskuren mit Schilddrüsenfütterung. Ibid.

16. Magnus-Levy: Ueber den respirat. Gaswech. unter dem Einfl. der Thyreoidea. B. k. W. **1895.** Nr. 30.

17. Loewy and Richter: Sexualfunktion und Stoffwechsel. Ar. P. **1899.** Suppl. 174 and zur wissenschaftl. Begründung der Organther. B. k. W. **1899.** Nr. 50.—Richter: Die prakt. Bedeutung der Organther. B. K. 139. 1900.

18. Loewy: Zur Physiol. der Geschlechtsorgane. Er. Ph. (Biochemie). **2.** 130. 1903.

19. Lüthje: Ueber die Kastration und ihre Folgen. E. A. **48.** 184. 1902 and **50.** 269. 1903.

20. Loewy and Richter: Zur Frage nach dem Einfl. der Kastration auf den Stoffwechsel. C. P. 22 Nov., 1902.

21. Oertel: Allge. Ther. der Kreislaufstörungen. 1884.—Schweninger and Buzzi: Die Fettsucht. S. m. A. Nr. 4. 1894.

22. v. Noorden: Ueber die Indikationen der Wasserbeschränkung bei Entfettungskuren. T. G. **2.** 155. 1900.—Nr. 2. P. 124.—Rosenfeld: Praxis der Entfettungskuren. D. Z. **1904.** Heft 1.—Salomon: Nr. 4.

23. Landauer: Ueber den Einfl. des Wassers auf den Organismus. U. A. M. **3.** 116. 1895.

24. Straub: Einfl. der Wasserentziehung auf den Stoffwech. Z. B. **38.** 537. 1899.

25. Ebstein: Fett oder Kohlenhydrate? 1885.—Oertel: Kritischphysiol. Besprechung der Ebstein'schen Behandl. der Fettleibigkeit. 1885; see also Discussion of IV. K. i. M. 1885. Pp. 9-69.

26. Hirschfeld: Beitr. zur Ernährungslehre des Menschen. Ar. p. A. **114.** 301. 1889.—Betrachtungen über die Voit'sche Lehre von dem Eiweissbedarf der Menschen. Ar. P. M. **44.** 428. 1889.—Klemperer: Über den Stoffw. und die Ernährung in Krankheiten. Z. M. **16.** 550. 1889.

27. v. Noorden and Dapper: B. p. G. 17 Feb., 1893.—Ueber den Stoffw. fettleibiger Menschen bei Entfettungskuren. B. k. W. 1894. Nr. 24.—Dapper: Stoffw. bei Entfettungskuren. Z. M. **23.** 113. 1893.—Dapper: Ueber Entfettungskuren. Ar. V. **3.** 1. 1898.

28. Hirschfeld: Behandl. der Fettleibigkeit. Z. M. **22.** 142. 1893.—

Ueber den Eiweissverlust bei Entfettungskuren. B. k. W. **1894.** 621.—Ueber den Nahrungsbedarf bei Fettleibigen. B. K. Heft 130. 1899.

29. Dapper: Nr. 27 (1898).

30. Pfeiffer: Behandl. der Fettleibigkeit in Pentzoldt-Stintzing's Handb. der spez. Ther. **2.** 11. 1897.—Magnus-Levy, Salomon: Nr. 4.—Dapper: Nr. 29.—Allard: Ueber den Einfl. eines natürl. Bitterwassers auf den Stoffw. Z. M. 45. 340. 1902.—Orgler: Ueber Entfettungskuren im Kindesalter. Mü. m. W. **1905.** 367.

31. Hellesen: Ueber den N-Stoffw. bei einem an Adipositas nimia leidenden Kinde. Ja. K. **47.** 389. 1903.

32. Grawitz: Zur Wirkung des Thyrojodins auf den Stoffw. bei Fettsucht. Mü. m. W. **1896.** Nr. 14.—Gluzinski and Lemberger: Ueber den Einfl. der Schilddrüsensubstanz auf den Stoffw. C. i. M. **1897.** Nr. 4.—Magnus-Levy: Nr. 4.

33. v. Noorden: Nr. 2. P. 60.

34. v. Noorden and Dapper: Nr. 27.—Ludwig: Ueber den Einfl. des Karlsbader Wassers auf den Stoffw. C. i. M. 1896. Nr. 45, 46.—Jacoby: Einfl. des Apentawassers auf den Stoffw. eines Fettleibigen. B. k. W. 1897. Nr. 12.—Rubner: Nr. 5.—Hellesen: Nr. 31.—Salomon: Nr. 4.

35. Heissler: cited by Grawitz: Klin. Pathol. des Blutes. P. 433. 1902.

36. Bouchard: Mal. par ralentissement de la nutrition. P. 114. 1890.

37. Kisch: Die Fettleibigkeit. 1888.

38. Oertel: Nr. 21. P. 36.

39. v. Noorden: Nr. 2. P. 47.

40. Leichtenstern: Über den Hämoglobingeh. des Blutes. P. 44. 1878.

41. Grawitz: Nr. 35. P. 434, and Dapper: Nr. 27 (1898).

42. Dennig: Die Bedeut. der Wasserzufuhr für den Stoffw. Z. d. p. T. **2.** 292. 1899.

43. Burmin: Alkaleszenz des Blutes bei pathol. Zuständen. Z. M. **39.** 365. 1900.

44. Cantani: Stoffwechselkrankh. III. Teil. 1881.

45. Leven: Les coefficients urinaires dans l'obésité. J. P. P. G. **3.** 405. 1901.

46. Setti: R. v. **16.** 113. 1899. Ref. in Ma. 1899. P. 742.

47. Cantani: Nr. 44. P. 36.—Kisch: Nr. 37. P. 128.—Bouchard: Nr. 36. P. 65.—Immermann: v. Ziemssen's Handb. d. spez. Path. XIII. **2.** 353. 1876.

48. Kisch: Zur Kenntnis der Oxalsäureaussch. bei Lipomatosis. B. k. W. **1892.** 357.—Ueber den Einfl. der Trinkkur mit alkal. Mineralwässern auf die Oxalsäureaussch. T. M. **1896.** 138.

49. v. Noorden: Path. des Stoffw. P. 178. 1893.

50. Mohr: Ueber Autointoxikationen mit Säuren. N. k. A. H. 4. P. 37. 1904.

51. Frerichs: Der Diabetes. P. 1886. 1884.—Seegen: Der Diab. mell. P. 127. 1893.—Bouchard: Nr. 36. P. 186.—Kisch: Nr. 37. P. 152.—v. Noorden: Die Zuckerkrankheit. P. 53. 1901.

52. Fleiner: In the Discussion in v. Strümpell's Vortrag: Zur Aetiol. des Diab. mell. Naturf.-Vers. 1896. W. k. W. **1896.** 934.—Hirschfeld: Ueber die Beziehungen zwischen Fettleibigkeit und Diabetes. B. k. W. **1898.** Nr. 10.

53. v. Noorden: Zur Frühdiagnose des Diab. mell. XIII. K. i. M. P. 481. 1895.—Nr. 2. P. 78.

54. Rubner: Nr. 5. P. 70.—Schattenfroh: Respirat. Versuche an einer fetten Versuchsperson. Ar. Hy. **38.** 93. 1900.—Broden u. Wolpert: Respirat. Arbeitsvers. an einer fetten Versuchsperson. Ibid. **39.** 298. 1901.

55. Crame..: Ueber die Beziehungen der Kleidung zur Hauttätigkeit. Ar. Hy. **10.** 231. 1890.—Dapper: Nr. 27 (1893).

56. Leubuscher: Ueber die Fettabsch. des menschl. Körpers. XVII. K. i. M. P. 457. 1899.

CHAPTER IV

THE RARER DERANGEMENTS OF CARBOHYDRATE METABOLISM

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The development of the chemistry of the carbohydrates owes much to the older observations relating to the occurrence of various kinds of sugar, or of their near derivatives, that have been found in human urine. Although none of these "non-diabetic" glycosurias is of the great practical importance of diabetes, still, collectively they are of considerable theoretical significance in the elucidation of carbohydrate metabolism and of the changes undergone by sugar in the process of assimilation.

The differential diagnosis between these conditions (which, according to recent observers, are by no means rare) and diabetes is not always easy, so that the possibility of mistaking any of them for true diabetes imparts a considerable practical interest to these anomalies. We commence with the commonest of these conditions, the excretion of fruit-sugar.

I.—FRUCTOSURIA.

1. Introductory.

In past literature a number of instances of low rotating urines capable of undergoing fermentation are described, in which the polarimetric and volumetric estimations of the amount of sugar revealed discrepancies that could be explained the most easily by assuming the presence of a lævorotating fruit-sugar along with glucose. Such observations have been published by Zimmer, Ventzke, Czapek, Worm-Müller, Seegen, Mauthner, Roehmann, Cotton, Personne, Henniger, Marie, and Robinson. The incompleteness of the methods then in use afforded no certain means of recognising fruit-sugar, so that the statements of the older observers must be accepted with reserve. The most characteristic indication, lævorotation, may also be occasioned by β-oxybutyric acid, conjugated glycuronic acid and amino-acids—substances which formerly were either not known, or were not sufficiently taken into consideration. In those cases in which glucose was also present confusion with these substances is quite possible, inasmuch as the behaviour with yeast would embarrass

the recognition of a second fermentable sugar. Seegen and Mauthner's case (1) can alone survive rigid criticism ; it was subsequently examined with great care by Külz (2), who, by applying Salkowski's copper-sulphate-alkali method with a large amount of urine, succeeded in isolating a sugar which very probably was lævulose.

Occurring at a later period, the observations of May (3) and Schlesinger (4) are most trustworthy. Still freer from doubt are the recent cases investigated with improved methods by Rosin and Laband (5), Lépine and Boulud (7), and also by Neubauer (24). The authors last named unmistakably determined the fruit-sugar either by analysis, or by isolating it in the form of a derivative—calcium fructosate [Herzfeld and Winter], methylphenylosazone[1] [Neuberg]. Neubauer obtained it as such in the crystalline form.

The statements referred to relate solely to the (so far) very limited number of cases of

2. Pure Lævulosuria,

in which titration and polarization yield almost identical results, and the presence of another kind of sugar can be excluded.

Pure lævulosuria occurs in persons of both sexes, and has been observed at all ages. The amount of fruit-sugar excreted appears to be subject to great variations. Schlesinger found 2·7 grammes a day ; Lépine found almost ten times as much—24 grammes.

Neubauer saw this form of lævulosuria disappear after complete withdrawal of carbohydrates, even of the ketoses.

Another kind of sugar may be present in the urine along with lævulose ; recent investigations show that cases of this kind are the most common, such as

3. Lævulosuria associated with Glycosuria.

Rosin and Laband, Dub, and Umber have directed attention to the frequent occurrence of this combination. Schwarz corroborates this by demonstrating the coexistence of lævulose with glucose in six out of nineteen cases. This combination has been met with in all forms of diabetes ; in a case of glycosuria in a child it was found by Umber twenty-seven times in twenty-eight successive days. In severe types of diabetes, in which acidosis occurs, Umber scarcely ever missed finding lævulose, especially when no restriction was imposed on the intake of carbohydrates.

Neubauer (24) observed some remarkable conditions in a case of mixed melituria. Withdrawal of carbohydrates caused both the fruit-sugar and the glucose to disappear from the urine. When lævulose was given, it was utilized (more than 50 grammes) ; on the other hand, glucose was

[1] Among the naturally occurring hexoses, the asymmetric methyl phenyl-hydrazin, $\begin{matrix}CH_3\\C_6H_5\end{matrix}\!\!>\!N\!-\!NH_2$, directly forms a methyl-phenyl-osazone with the ketose, fruit-sugar, alone. With the isomeric aldehyde sugars it only forms, as a rule, the easily distinguished hydrazone. Nevertheless, the reaction is only infallible when carried out under specific conditions (8).

less completely used up (only 15 to 25 grammes) ; in part it was excreted as lævulose.

In mixed melituria the quantity of fructose excreted is usually less than that of grape-sugar ; but as there is great difficulty in determining the respective amounts of these sugars when present together, only a few exact statements are recorded.

Instances in which glycosuria and fructosuria alternate have not been recognised with certainty. Cases of the nature of those recorded by Späth and Weil (25) have not yet been explained ; in these cases a second lævorotating, reducing substance was excreted along with lævulose ; it was unfermentable, and yielded no osazone. Probably these cases have no relation to intrinsic diabetes.

A third category is represented by the occurrence of

4. Alimentary Fructosuria.

This condition has long been known, and may occur in healthy persons, as well as in those who suffer from diabetes or other disease. In healthy people unmistakable cases of alimentary lævulosuria have been described by Moritz, Haycraft, and H. Strauss (10). Naunyn, Seegen, Cotton, le Goff, Weintraud, Laves, Socin, Umber, Schlesinger, and Schwarz (11) have observed it in various degrees of persistent diabetes. The quantities of fruit-sugar excreted in the alimentary lævulosuria of the diabetic obviously depend upon the amount of fructose administered and the varying tolerance in each case. Umber (9) observed the daily excretion in a case of severe diabetes to equal 259·5 grammes ; this, by the administration of 100 grammes of lævulose, was increased to 377·5 grammes, of which 25·17 grammes were fruit-sugar—that is to say, one-fourth of the amount of lævulose administered. In other diseases, also, beside diabetes —for example, in diseases of the liver—the assimilation of fruit-sugar may be extraordinarily diminished, whether given free as disaccharide (cane-sugar) or as polysaccharide (inulin) ; any difference thus occasioned is only quantitative. In relation to diagnosis, the observation first made by H. Strauss (12) that alimentary lævulosuria may constitute a direct indication of functional derangement of the liver is important. The accuracy and suitableness of Strauss's method of testing the liver function have been confirmed by Sachs, Chajes, Lépine, Baylack and Arnaud, Bruining, and others (13).

In other functional derangements of important organs, or when they are experimentally damaged, alimentary lævulosuria occurs under slight provocation. Porges (14) saw it in the dog, after poisoning with thyroid-gland substance ; in stoppage of the common bile-duct and in pneumonia it was observed by Umber ; and by Hans Sachs in frogs after removal of the liver. Numerous experiments on animals show that by damage to the liver the tolerance for fruit-sugar is diminished.

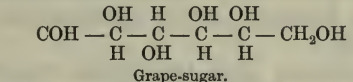
In connection with the relation between alimentary lævulosuria and the hepatic function already mentioned, Schröter (23) has drawn attention to the occurrence of alimentary lævulosuria in eclampsia, in which Schmorl has frequently found necroses in the liver. There is no ground, however,

for assuming a real connection between the excretion of fruit-sugar and eclampsia. On the other hand, it appears that alimentary lævulosuria is a frequent accompaniment of pregnancy ; it was observed in 17 out of 95 pregnant women, in 8 out of 18 lying-in women, and in 3 out of 6 women in labour. Brocard (20) believes that spontaneous lævulosuria occurs in some pregnant women ; he also regards the alimentary lævulosuria of pregnancy as a special anomaly, and not as the result of an affection of the thyroid gland, which frequently occurs in the gravid state (*vide* No. 14).

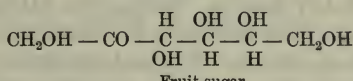
5. Etiology and Theory of Lævulosuria.

Whilst alimentary lævulosuria may be due to the natural assimilation limit being exceeded, or to a lowering of the power of oxidation, such an explanation cannot be accepted either for pure fructose diabetes or for the mixed glucose and lævulose diabetes. After copious ingestion of fruit-sugar and other carbohydrates, or even glucose, Rosin and Laband, and also May, failed in their cases of spontaneous lævulosuria to cause an increase in the excretion of lævulose, or to determine the occurrence of any other sugar. Umber observed a slight effect in a case of severe diabetes, in which lævulose was also present in the urine ; 100 grammes of lævulose were given, and were almost entirely excreted as grape-sugar. That is to say, in the opinion of Minkowski and Naunyn, the lævulose was transformed beyond the glycogen stage into blood dextrose. The lot of the lævulose polysaccharides, of inulin, is precisely the same [Umber].

The indubitable development of lævulose in the organism, previously difficult to explain, has lost some of its puzzling aspect through the researches of Lobry de Bruyn and Alberda von Eckenstein ; these chemists show that glucose and lævulose change the one into the other proportionally to their dissociation by the action of hydroxyl ions, especially by traces of alkalis, and also by neutral salts such as sodium acetate.



Grape-sugar.



Fruit-sugar.

Rosin (15) observed a like transformation of grape-sugar into lævulose by prolonged heating in dilute hydrochloric acid. This important observation is confirmed by Ost (16).

Neuberg and Mayer (17) have experimentally proved with another sugar—mannose—that similar atomic displacements take place in the animal economy ; the possibility, therefore, of a formative process of this kind taking place in the body[1] is not to be rejected. The researches of

[1] In his dissertation (Strassburg, 1899), J. Baer directs attention to the errors which may be fallen into through a like transformation of glucose into fruit-sugar by systemic fluids, etc., with chemical manipulation outside the body.

Neuberg and H. Strauss (18) actually show that without previous ingestion of lævulose fruit-sugar may be present in the human body. Gürber and Grünbaum observed a like power in the amniotic fluid of the cow, the she-goat, and the sow, but not in that of mankind. Rosin and Laband obtained proof of the presence of fructose in the arterial blood of their patient with spontaneous lævulosuria, as in the common excretion of glucose and fructose. The excretion of lævulose is more difficult to account for than its occurrence. In relation to this question, it is to be remembered that F. Voit and E. Voit, after subcutaneous administration, observed that fruit-sugar, as compared with glucose, more easily found its way into the urine ; and that C. von Voit and Cremer (20) proved that it possessed a feebler capacity to become stored-up glycogen. It is, further, to be remembered that the statement made in 1851 by Bouchardat (often erroneously attributed to Külz) as to the specially easy way in which lævulose is burnt up is no longer accepted without question, as shown in the recent investigations by Naunyn, Schwarz, Lion, and especially by Schlesinger. To say the least, great individual differences exist in the tolerance of fruit-sugar, which is much less than that for grape-sugar. It depends in an important degree upon the nature of the other food partaken of, and upon the extent to which it is utilized in the organism [Falta (21)]. Minkowski's researches on a dog which had been deprived of its pancreas undoubtedly show that lævulose is metabolized, whilst glucose is not ; under such conditions, therefore, lævulose is capable of forming glycogen, and glucose is not.

It is remarkable how extremely resistant lævulose is to the sugar-destroying action of most organs (glycolysis). Sehrt (21) found that a mixture of pancreas and muscle, which acted energetically on grape-sugar, was powerless with fruit-sugar.

We have no certain knowledge as to whereabouts in the organism the formation of lævulose takes place ; the experiments previously mentioned relating to the metabolism of lævulose show that the liver exercises a direct or indirect influence, and it is not impossible that this organ, the many-sided chemical laboratory of the organism, also participates in the production of lævulose.

Only a few statements have been made concerning the influence phlorizdin exercises in lævulosuria. Schlesinger (4) found in his patient, as in the healthy person, glucose, but no lævulose appeared. On the other hand, Neubauer (24), in his case of mixed melituria, observed that both fruit-sugar and glucose were excreted after subcutaneous injection of phlorizdin, whilst when it was given by the mouth no effect was produced.

The etiology of spontaneous lævulosuria is unknown ; as a rule, it manifests itself by typical diabetic symptoms—polyuria, thirst, irritation of the skin, etc. ; any relation to other diseases is uncertain. In Rosin's and Laband's case there was obesity ; in May's case there was transverse myelitis. Lépine observed lævulosuria after an abortion. In Mauthner and Seegen's case, and also in the somewhat doubtful case of Czapek and Zimmer, hereditary disposition to diabetes seemed to be present. Neubauer reports synchronous manifestations affecting the nervous system—neurasthenia, melancholia, and neuralgia.

The excretion of fruit-sugar may occur in all stages of existing glycosuria ; according to Umber, it is almost constantly present in the severest cases of diabetes if improper diet is taken.

Compare lævulosuria in the chapter on Diabetes Mellitus.

6. Therapy.

No therapeutic treatment is known for a disease like pure lævulosuria, which possesses so few intrinsic characteristics. The excretion of fruit-sugar can almost always be diminished or abolished by limiting or entirely withdrawing carbohydrates, as is the case with glycosuria [Lépine] ; occasionally, indeed, simple withdrawal of ketoses suffices [Neubauer]. The effect is all the more readily produced, as, according to our present experience, lævulosuria, unlike ordinary diabetes, has no tendency to advance, but rather tends to improve.

In combined fruit and grape sugar excretion the first-named disappears coincidently with the diminution and cessation of the glycosuria [Schwarz, Umber].

7. Diagnosis of Lævulosuria.

1. Cases of pure lævulosuria are recognised by lævorotation of the urine, which possesses reducing properties, and is capable of undergoing fermentation. After fermentation with yeast, the urine loses its reducing and optical properties.

2. With concurrent glycosuria, the presence of lævulose is indicated by a considerable difference between the results obtained by polarization and titration. The capacity to undergo complete fermentation, with loss of reducing and rotating power of the resulting liquid, establishes the diagnosis. In all cases corroboration should be obtained by recourse to Seliwanoff's reaction—a red coloration of the urine—or warming it with resorcin and hydrochloric acid. It is necessary, however, to perform the test with certain precautions (22).

LITERATURE.

1. Seegen : Ein Fall von Lävulose im diabet. Harn. C. m. W. **1884.** 753.—Mauthner : Ibid.

2. Külz : Ueber das Vorkommen einer linksdrehenden wahren Zuckerart im Harn. Z. B. **27.** 228. 1890.

3. May : Lävulosurie. D. Ar. M. **57.** 279. 1896.

4. Schlesinger : Lävulosediabetes. Ar. P. P. **50.** 1. 1903.

5. Rosin and Laband : Z. M. **47.** 182. 1902.

6. Lion : Zur Frage des gleichzeitigen Auftretens von Fruchtzucker und Traubenzucker im Harn. Mü. m. W. **1903.** Nr. 26.

7. Lépine et Boulud : Sur un cas de diabète lévulosurique. Re. m. **24.** 185. 1904.

8. Neuberg : Ueber die Isolierung von Ketosen. B. C. G. **35.** 359 and 2626. 1902. Z. p. C. **45.** 359. 1905.—Ofner : Nachweis von Fruchtzucker in menschl. Körpersäften. Ibid. **45.** 359. 1905.

9. Dub : Beitr. zur Aussch. von Lävulose im Harn Diabet. Diss. Berl., 1902.—Umber : Ueber Aussch. und Assimil. von Fruchtzucker. Salkowski Festschr. 1904. 375.

10. Moritz: Ueber alimentäre Glukosurie. C. i. M. **12.** Nr. 28. P. 81. 1891.—Haycraft: Lävulose bei Diabetikern. Z. p. C. **19.** 137. 1894. —Strauss: Die Funktionsprüfung der Leber. D. m. W. **1901.** Nr. 44, 45.

11. Socin: Lävulose und Milchzucker bei Diabetes. Diss. Strassb. 1894.—Schwarz: Untersuch. über Diabetes. D. Ar. M. **76.** 279. 1903.

12. Strauss: See Nr. 10.—Ueber den Einfl. der verschied. Zuckerarten auf die Zuckeraussch. beim Menschen. B. k. W. **1898.** Nr. 18.

13. Sachs: Ueber die Bedeutung der Leber für die Verwertung der verschied. Zuckerarten im Organismus. Z. M. **38.** 87. 1899.—Lépine: La lévulosurie aliment. dans ses rapp. avec les affections du foie. Se. m. **1901.** Nr. 4. P. 105.—Baylack and Arnaud: Franz. Kongr. f. inn. Med. zu Toulouse, 1902.—Bruining: Zur Frage der aliment. Glukosurie bei Leberkranken. B. k. W. **1902.** Nr. 25. 587.—Chajes: Ueber aliment. Lävulosurie bei Leberkranken. D. m. W. **1904.** Nr. 19. P. 696.

14. Porges: Exper. Beitr. zur Wirkung und Nachwirkung von Schilddrüsengift. B. k. W. **1900.** P. 300. Nr. 14.

15. Rosin: Ueber Fruchtzuckerdiab., etc. Salkowski-Festschr. **1904.** 105.

16. Ost: Umwandlung der Lävulose in Dextrose. Z. C. **18.** H. 30. 1905.

17. Neuberg and Meyer: Ueber das Schicksal der drei Mannosen im Kaninchenleibe. Z. p. C. **37.** 530. 1903.

18. Neuberg and Strauss: Vorkommen von Fruchtzucker in den menschl. Körperflüssigkeiten. Ibid. **36.** 227. 1902.

19. Gürber and Grünbaum: Ueber das Vorkommen von Lävulose im Fruchtwasser. Mü. m. W. **1904.** Nr. 9.—Gürber: Ueber Zucker im Fruchtwasser. C. P. **19.** 315. 1905.—Grünbaum: Untersuch. des Fruchtwassers. V. W. G. **37.** 130. 1904.

20. Voit: Die Glykogenbild. aus Kohlenhydraten. Z. B. **25.** 543. 1889.—Voit: Über das Verhalten der verschied. Zuckerarten im menschl. Organ. bei subkutaner Injektion. D. Ar. M. **58.** 523. 1897.—Voit: Ueber die Glykogenbild. nach Aufnahme versch. Zuckerarten. Z. B. **28.** 245. 1891.—Cremer: Physiol. des Glykogens. Er. Ph. **1.** 803. 1902.

21. Sehrt: Zur Frage der hepatogenen Lävulosurie. Z. M. **56.** H. 5 and 6. P. 509. 1905.—Falta: Zur Klinik des Diab. mell. K. S. **1903.** Nr. 22.

22. Rosin: Eine Verschärfung der Seliwanoff'schen Reaktion. Z. p. C. **38.** 555. 1903.—Adler: Reaktion des Harns bei Behandl. mit Resorzin. Z. p. C. **41.** 206. 1904.—Ofner: Zur Kenntnis einiger Reaktionen der Hexosen. S. W. A. **113.** Abt. II. Apr., 1904.

23. Schröter: Ueber den Kohlenhydratstoffw. und aliment. Lävulosurie in der Schwangerschaft. Z. G. G. **56.** H. 1. 1905.

24. Neubauer: Zur Kenntnis der Fruktosurie. Mü. m. W. **1905.** Nr. 32.

25. Späth u. Weil: K. W. **72.** P. 717. 1902.

26. Brocard: Die Glukosurie der Schwangerschaft. C. r. S. B. **50.** 1077. 1898.

27. Minkowski: Uber Diab. mell. nach Exstirp. des Pankreas. Ar. P. P. **31.** 158. 1893.

II.—PENTOSURIA AND OTHER KINDS OF EXCRETION OF FIVE-CARBON SUGARS.

1. Intrinsic Pentosuria.

In the year 1892 E. Salkowski, along with M. Jastrowitz (1), discovered a new anomaly in human metabolism—a distinct kind of diabetes, in which no glucose, but a carbohydrate of the five-carbon series, a pentose, was excreted. Two other cases of the same kind were soon after communicated by E. Salkowski and F. Blumenthal (2); since then a number of others have been met with. The later observations are by Reale [4], Colombini [5], Meyer [6], Bial [7-11], Brat [12], Luzzatto [13], d'Amato [14], Bendix [15], Romme [16], and von R. and O. Adler [17] (3).

The statements of different writers as to the amount of pentose present in the urine range between 0·08 and 1·0 per cent. ; but, for reasons given below, these estimations are too low, the true percentage being about double that which is stated. Urine containing pentose possesses reducing properties, which, however, are usually of a peculiar kind ; the Fehling's solution at first remains clear, and then, after boiling for a time, is suddenly reduced. Pentose urine is incapable of fermentation, and, with the exception of one case (14), has never been found to possess optical activity. Up to a certain point, the positive reaction with Tollen's orcin test is characteristic green coloration on heating the urine with orcin and hydrochloric acid ; an amyl-alcohol extract of this yields an absorption band between C and D. Similar treatment with phloroglucin gives a red coloration, and the amyl-alcohol extract shows a band between D and E. These reactions, however, also occur in urines which contain no pentose, but only glycuronic acid.

The clinical portrayal of pentosuria, if such a thing can be spoken of, resembles diabetes in one respect only—namely, that the person so affected excretes sugar in the urine for years. There are no intrinsic clinical appearances, as in true diabetes. Although occasionally nervous symptoms are mentined in the clinical history of solitary pentosurics, there is, according to Blumenthal and Umber (18), no occasion for therapeutic treatment ; apart from the anomaly as such, most pentosurics are quite healthy. It must be mentioned, however, that in Case 10 the pentosuria was proved to have occurred after prolonged cocainism, and that Cases 1 and 4 were addicted to morphinism ; still, no proof is afforded of any causal relation between the abuse of the alkaloids and the irregularity of metabolism, for chronic pentosuria lasted after withdrawal of the alkaloids.

It is noteworthy that the tendency to pentosuria may be hereditary. Brat (3) narrates a case of pentosuria affecting two members of a family—a woman sixty-two years old, and her brother aged fifty. Blumenthal's two cases (2) were brother and sister, and Bial observed pentosuria in two sisters and their brother (3).

In conformity with the absence of clinical symptoms, this anomaly of metabolism usually occasions no suffering to those who are the subjects of it ; for the most part, the discovery of pentosuria is accidentally made in the course of a special scientific examination of the urine. Not withstanding this, the anomaly claims the careful attention of the practitioner ; for, even in inexpert hands and by superficial examination, it is quite possible to obviate confusion with diabetes, and thus to spare the pentosuric unnecessary dietetic restrictions.

The practical interest in pentosuria, however, is greatly surpassed by its theoretical importance (5), which is due to the nature of the excreted sugar, apart from the existence of an anomaly of carbohydrate metabolism in the five-carbon series. According to the investigations of C. Neuberg (6), the sugar excreted is the optically inactive, racemic arabinose. It is a well-known phenomenon that living tissues of every kind produce, without exception, optically active forms, and by means of a component render active any racemic forms which are administered. The occurrence of an inactive urinary pentose is the first instance of the appearance of a

racemic body in the animal organism. The constitution of urinary pentose characterizes pentosuria as a condition *sui generis*. The source whence the urinary pentose springs must be in the organism itself, as no inactive arabinose is taken as food [Neuberg]; besides, Neuberg and Wohlgemuth (20) have shown that ready-formed inactive arabinose undergoes such changes in the healthy organism that it appears in the urine as *d*-arabinose. In like manner, Blumenthal and Bial (7), by means of investigations on the metabolism of a pentosuric, have established the independence of pentosuria and the food partaken of, especially as regards the presence in it of the pentose group of vegetable and animal origin. It is noticeable that in pentosurics the assimilation of other carbohydrates is unchanged, and that even the ordinary *l*-arabinose is utilized as in health. The presence of urinary pentose in the blood has not been satisfactorily proved [*cf.* P. Mayer (19)].

It is well known that a pentose-containing nucleo-proteid occurs in the animal organs. From the pancreas, which is specially rich in it, Hammarsten (8) and E. Salkowski (9) obtained a pentosazon, the constitution of which, however, is different from that of urinary pentose. Neuberg (10) and Wohlgemuth (11) showed that the pentose derived from animal organs is *l*-xylose. There is no possible connection between these two sugars, *r*-arabinose and *l*-xylose, quite apart from the fact that the total store of pentose in the human organism, according to Grund (12), only amounts to about 10 grammes, whilst the quantity of urinary pentose daily excreted may be three and a half times as much, or 30 to 36 grammes.

Urinary pentose, therefore, is formed in the organism of the pentosuric. It is conceivable that galactose is the ultimate source of urinary pentose. Certain chemical and biological experiences, as well as analogical conclusions, are in favour of this view [Neuberg (13)]; but no proof in support of it has yet been advanced. An artificially produced, genuine pentosuria has so far not been obtained.

It is specially noteworthy that in the urine of the pentosuric alone in nature does five-carbon sugar exist in the *free*, monomolecular, reducing state. Both in the vegetable and the animal kingdoms it is found only in the form of a high molecular anhydride or complicated glucoside, as pentosane or in nucleo-proteids. From these it can only be set free by a more or less profound hydrolytic cleavage, which in the animal organism (so far as is known) can only be accomplished by special specific enzymes [Neuberg and Milchner]. Nevertheless, the statement regarding the existence of urinary pentose in the free, reducing form demands a certain limitation. It is true that, contrary to the condition of all other naturally-occurring pentoses, urinary pentose is monomolecular, but still, only in part is it in the free form. According to recent researches by C. Neuberg (5), a definite portion is combined with urea in the form of a ureid :

$$CH_2OH—CH.OH—CH.OH—CH.OH—CH : N.CO.NH_2.$$

The ureid only reduces Fehling's solution after having undergone cleavage, and this in part occasions the peculiar attitude of pentose-

containing urine towards the reduction test. In titration the part of the pentose which is combined with urea is withheld from the estimation, and only manifests itself after cleavage by being boiled with 5 per cent. sulphuric acid. This behaviour is of importance, inasmuch as the statements relating to the amount of racemic arabinose in pentose urine are almost all 100 per cent. too low.

2. Cases of the Excretion of Various Pentoses.

As already mentioned, in all cases of pentosuria except one, the sugar or its derivative has always been found to be optically inactive. An exception is recently described by Luzzatto (14). This author assumes the excretion of *l*-arabinose entirely independent of its reception in food. A case in which the excretion of *r*-arabinose was probably accompanied by dextrorotating *l*-arabinose has already been mentioned by F. Blumenthal (17). It appears doubtful whether Luzzatto's case is to be classified with the other examples of genuine chronic pentosuria, or that it represents the first instance of a new anomaly of metabolism. It certainly cannot be numbered with the cases of alimentary pentosuria, in which, as is well known, an optically active pentose is excreted. Such cases were first observed by F. Blumenthal (15); certain people after eating fruit which contains much pentose (cherries, plums) excrete pentose having reducing properties, mostly *l*-arabinose. Barczewsky (16) has made similar observations. A recent case communicated by R. von Jaksch (16) is especially noteworthy. It relates to the excretion of an inactive arabinose after the ingestion of apple-juice, which contains pentose. The optical inactivity of a five-carbon sugar in the urine is remarkable, seeing that in fruit active pentoses alone occur.

Differing from intrinsic pentosuria is the excretion of small amounts of sugar of the five-carbon series, which, according to Külz and Vogel (17), occasionally accompanies the output of grape-sugar in severe diabetes. The same authors have observed (17) that in dogs the extirpation of the pancreas is followed by the excretion of a pentose which is not dependent on the composition of their food. The nature of this five-carbon sugar, and the clinical signification of its appearance, are unknown.[1]

3. The Diagnosis of Essential Pentosuria.

Pentosuria is indicated by the urine possessing reducing properties, possibly of a dilatory kind, with absence of fermentable capacity and of optical activity. Positive reactions with the orcin and phloroglucin tests, and the production of a phenylosazon with a melting-point of 160° to 166° C., strengthen the assumption.

Supplementally, attention may be directed to the statement of Brat (21) relating to the occurrence of *methylpentoses*, or, more accur-

[1] For further details concerning the physiology of the pentoses, see C. Neuberg, "Ergebnisse der Physiologie," III., 1 Abteil, S. 373-452 (1904). Compare also Vol. I., p. 159, and Vol. III., p. 576.

ately, of methylpentosanes, in human urine. Nothing further is known either of the nature of the excreted carbohydrate, or of the conditions under which it appears. Most probably it represents in the urine the spent products of vegetable food, in analogy with the behaviour of pentosanes, which occasionally appear to pass over in small amount into the urine.

LITERATURE.

1. Salkowski and Jastrowitz: Ueber eine bisher noch nicht beobachtete Zuckerart im Harn. C. m. W. **1892.** Nr. 19. P. 337.—Salkowski: Ueber das Vorkommen von Pentosen im Harn. Z. p. C. **27.** 507.

2. Salkowski: Ueber die Pentosurie. B. k. W. **1895.** Nr. 17. P. 364.—Blumenthal: Über Pentosurie. B. k. W. **1895.** Nr. 26. P. 567.

3. Reale: Fall von Pentosurie bei einem Morphinisten. R. c. **26.** Nr. 3. 1894. C. i. M. **15.** 680. 1894.—Colombini: Pentosurie und Xanthoma diabet. Mo. D. **24.** Nr. 3. P. 129. 1897.—Meyer: Ueber chron. Pentosurie. B. k. W. **1901.** Nr. 30. P. 785.—Bial: Ueber Pentosurie. Z. M. **39.** H. 5, 6. P. 473. 1900.—Bial: Ueber das Vorkommen von Pentosurie als familiäre Anomalie. B. k. W. **41.** 552. 1904.—Brat: Pentosurie und Pentosenreaktion. Z. M. **47.** H. 3, 4. P. 499. 1902.—Luzzatto: Contrib. alla conoscenza ed allo studio della pentosuria cronica. A. F. s. I. **7.** 1902.—D'Amato: Pentosuria. R. C. C. III. **26.** 1902.—Romme: P. m. **1901.** 27 Juli.—Bendix: Ein Fall von Pentosurie. Mü. m. W. **1903.** Nr. 36. P. 1551.—Adler: Zur Kasuistik der Pentosurie. Ar. P. M. **110.** 625. 1905.

4. Salkowski: Ueber das Vorkom. der Pentaglukosen im Harn. C. m. W. **1892.** Nr. 32. P. 593.

5. Neuberg: Physiol. der Pentosen und der Glukuronsäure. Er. Ph. III. I. Abt. 373-452. 1904. (Literature of 1904.)

6. Neuberg: Die Harnpentose. Ein optisch-inaktives natürliches Vorkommen der Kohlenhydrate. B. C. G. **33.** 2243. 1700.

7. Bial u. Blumenthal: Chronis. Pentosurie. D. m. W. **1901.** Nr. 22. P. 349.

8. Hammarsten: Zur Kenntnis der Nukleoproteïde. Z. p. C. **19.** 28. 1894.

9. Salkowski: B. k. W. **1895.** Nr. 17. P. 364.

10. Neuberg: Die Konstitution der Pankreasproteïdpentose. B. C. G. **35.** 1467. 1902.

11. Wohlgemuth: Ueber das Nukleoproteïd der Leber. Z. p. C. **37.** 475. 1903.

12. Grund: Ueber den Gehalt des Organ. an gebundenen Pentosen. Z. p. C. **35.** 111. 1902.

13. Neuberg: Die Pentosen des Tierkörpers. B. p. G. Jahrg. **1901-1902.** Nr. 10, 11.

14. Luzzatto: Ein Fall von Pentosurie mit Aussch. optisch-aktiver Arabinose. Be. P. P. **6.** 87. 1905.

15. Blumenthal: Path. des Harns. **1903.** P. 388.

16. Barczewsky: Gazetta Lekarska. **1897.** Nr. 22.—v. Jaksch: Ueber eine bisher nicht beobachtete Quelle der aliment. Pentosurie. C. i. M. **27.** 145. 1906.

17. Külz u. Vogel: Ueber das Vorkommen von Pentosen im Harn bei Diab. mell. Z. B. **32.** 185. 1895.

18. Blumenthal: D. K. III. 309, 314. 1902.—Umber: Die Pentosurie. T. G. **1902.** Nr. 1. P. 20.

19: Mayer: Ueber eine bisher unbekannte reduzierende Substanz des Blutes. Z. p. C. **32.** 518. 1901.

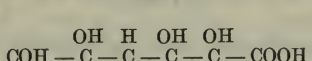
20. Neuberg u. Wohlgemuth: Ueber das Schicksal der drei Arabinosen im Kaninchenleibe. Z. p. C. **35.** 41. 1902.

21. Brat: Zur Kennt. der Pentosurie und der Pentosenreak. Z. M. **47.** 502. 1902.

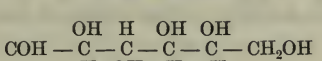
III.—THE EXCRETION OF GLYCURONIC ACID.

1. Discovery and Chemical Character.

In the year 1878 glycuronic acid was simultaneously discovered by M. Jaffé, O. Schmiedeberg, and Hans Meyer, as a product of animal metabolism. The relation it bears to grape-sugar was assumed by its discoverers, and was proved in 1891, when Emil Fischer and Piloty effected the synthesis of glycuronic acid. The two substances have the same relation to each other that aldehyd-alcohol has to aldehydic acid.

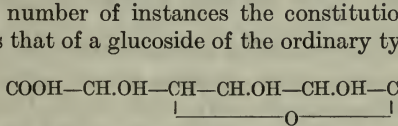


Glycuronic Acid.



Grape-sugar.

It is characteristic of glycuronic acid that, when produced naturally, it is never found in the free state, but only in the combined form as conjugated glycuronic acid. This acid is specially capable of entering into combination with a great number of substances which almost without exception have the chemical characteristics of an alcohol or a phenol. The conjugated glycuronic acid compounds possess a further common characteristic : they are lævorotatory, whilst free glycuronic acid is dextrorotatory. By treatment of the conjugated acid with acids and other hydrolyzing agents, free glycuronic acid and its conjugate are produced. In the greater number of instances the constitution of conjugated glycuronic acids is that of a glucoside of the ordinary type :



Still, other types of the combination occur [Jaffé]. A number of physiologically important representatives of this class of the glucoside type have been determined by the synthesis of conjugated glycuronic acids, carried out by Neuberg and Neimann, and by the same authors' discovery of the power of cleavage possessed by enzymes (emulsin and kefirlactase) on the conjugated acids.

2. The Occurrence of Glycuronic Acid Combination in the Normal State.

The excretion of glycuronic acid compounds under artificially produced conditions has been known for many years, but as a product of normal and pathological human metabolism its discovery is quite recent.

(*a*) *Urine.*

Some of the older authors had inferred the presence of small amounts of conjugated glycuronic acid in normal urine, but its occurrence was first shown by Mayer and Neuberg (2). By working with 50 litres of normal urine, glycuronic acid was isolated, and the nature of its conjugates was established. They are phenol and indoxyl, or cresol and scatoxyl. The amount of glycuronic acid reaches at least 0·004 gramme in 100 c.c. of urine.

(*b*) *Blood.*

Subsequently Paul Mayer found glycuronic acid to be a normal constituent of blood, and isolated it out of the blood of oxen. This discovery was confirmed by Lépine and Boulud (2) with human blood and the blood of dogs and rabbits. The nature of the conjugate has so far not been discovered.

(*c*) *Organs.*

As a rule, very little glycuronic acid is found in the organs in which we assume it to be formed. Lépine in one instance demonstrated its presence in the liver. The statements of Bial, Huber, and van Leersum concerning the presence of glycuronic acid in the normal contents of the bowel are the result of confusion of it with pentosane, or with nucleoproteid containing pentose. On the other hand, the administration of a conjugated glycuronic acid seems to be followed by the appearance of aldehydic acid in the bile. In accordance with the older views, Béla von Fenyvessy (4) observed that the total conjugated glycuronic acid is excreted in the urine.

The older statements concerning the occurrence of conjugated glycuronic acid in other parts of the organism are not confirmed by recent researches. Chondroitin sulphuric acid, which results from the breaking down of cartilaginous substances, yields, according to Schmiedeberg, glycuronic acid as a cleavage product; but according to Orgler and Neuberg, the acid which is thus produced contains nitrogen, and is probably a poly-oxy-amino acid. It is not yet determined whether the glycothionic acids—that is, conjugated sulphuric acids which contain nitrogen, and include a carbohydrate group—are related to glycuronic acid [Mandel and Levene (5)]. Such a relation with sarco-phosphoric acid, and presumably with uro-proteic acid, is to be denied.

It is to be inferred from the above statements that the amount of conjugated glycuronic acid in the normal organism is inconsiderable, and probably its presence is not constant. This holds good especially for the glycuronic acid combinations of the urine, the amount of which depends on the digestive conditions then existing in the intestines; in other words, it is determined by the quantity of phenol and indol that is produced.

3. Artificially-developed Glycuronic Acid Excretion.

The excretion of glycuronic acid artificially produced is of great practical interest, and in its quantitative aspect is almost as striking as the scanty amount that is excreted in the normal. The number of substances which are capable of producing the excretion of glycuronic acid is legion. This is not the place to enumerate them ; let it suffice to say that almost every class of organic combination can furnish representatives capable of conjugating with glycuronic acid. The practical importance of this arises out of the fact that quite a large number of important therapeutic agents are glycuronic acid producers : such are chloral hydrate, carbolic acid, resorcin, antifebrin, phenetidin, menthol, borneol, camphor, sandal-oil, β-naphthol, chinosol, morphine, antipyrin, pyramidon, etc. These combinations undergo many changes in the organism, so that what may be called in a certain sense alimentary glycuronuria may be broadly classified according to the following arrangement :

1. *Alcohols and phenols* and bodies which include an alcoholic hydroxyl (—OH) are capable of directly conjugating with glycuronic acid ; such are ethyl alcohol, carbolic acid, chinosol.

2. *Aldehydes*, which are first reduced to primary alcohols—as chloral hydrate, trichlorbutylaldehyde.

3. *Ketones*, which are first changed into secondary alcohols — as acetone, diacetic acid.

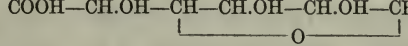
4. *Carbohydrates*, which are hydrolyzed into alcohols or phenols—as benzole, naphthalin.

5. *Heterocyclic* substances behave similarly, and are also hydrolyzed —as indol, antipyrin.

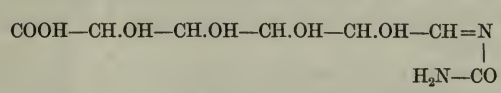
6. *Hydroaromatic* bodies of the camphor and terpene groups, which sometimes follow like rules, sometimes special rules.

In addition, a molecular diminution from oxidative breaking down or a molecular augmentation from synthesis may occur.

The result of all these various transformations is in each instance the formation of an alcohol or a phenol, which, with glycuronic acid, forms conjugated glycuronic acid. As already mentioned, these conjugated acids are mostly of the glucoside type :



The lævorotating urea-glycuronic acid obviously has a different constitution :



According to Neuberg and Neimann (6), this combination may be present in many urines which contain glycuronic acid without a corresponding amount of conjugates possessing alcohol and phenol characteristics (*vide* pp. 723 and 735).

[1] R stands for "radicals," such as phenyl, benzoyl, iso-propyl, etc.

Mention has already been made of the glycuronic acid combination isolated out of urine by means of the *p*-dimethylaminobenzaldehyde process of Jaffé (6), which probably also has a different constitution.

It is not possible to pronounce *a priori* concerning the capacity of a substance to conjugate with glycuronic acid ; each one must be determined by experiment. Substances which have a close chemical relationship frequently behave themselves in an absolutely contradictory manner —as, for example, *m*- and *p*-cymol (6), menthol and pulegon, nerol and geraniol (6). Only the first-named of each pair conjugate with glycuronic acid ; the isomers are split up by oxidation.

The range of glycuronic acid conjugation also covers wide limits. According to O. Neubauer (6), the proportion of the substance that is introduced which enters into combination with glycuronic acid is, with pure aliphatic substances, usually very small, but with halogen substitution products—for example, chloral hydrate—is very considerable. Extraordinary differences are met with in the extent of glycuronic acid conjugation in various animal species. Generally speaking, the formation of conjugated glycuronic acid in the herbivora is much more copious than in the carnivora. In many instances the herbivora alone are capable of accomplishing the synthesis. Human beings who live on a mixed diet take an intermediate position.

4. The Behaviour of Enzymes and Bacteria towards Glycuronic Acid.

Free glycuronic acid does not ferment with yeast. In small amount, possibly, along with much grape-sugar, it may—like pentose—be fermentable [Daiber (7)]. In opposition to this statement accepted by the older writers, Hildebrandt (7) has recently found free glycuronic acid to be fermentable by yeast or zymin with the production of carbon dioxide, and, in the place of alcohol, acetic acid and malonic acid. According to Thierfelder (7), glycuronic acid is decomposed by the microbes of sewage with a kind of methane fermentation that produces as by-products carbon dioxide, hydrogen, acetic and lactic acids. Many conjugated glycuronic acids have also very feeble power of resistance to putrefaction.

Under other conditions bacterial decomposition of glycuronic acid may be produced without complete rupture of the carbon chain. Salkowski and Neuberg (7), by means of the ordinary putrefactive microorganisms of flesh, in a feeble alkaline medium, produced cleavage of carbon dioxide from glycuronic acid, by which it was transformed into a pentose—*l*-xylose.

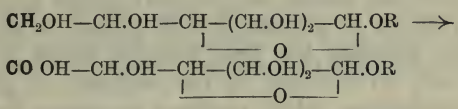
This biochemical transformation of glycuronic acid probably indicates one of the physiological functions which the acid fulfils in the organism. As was mentioned with regard to pentosuria, the five-carbon sugar of the organism is *l*-xylose ; on the other hand, glycuronic acid is chemically and physiologically closely related to grape-sugar, out of which it is produced in the organism. In all probability, therefore, as a normal constituent of the blood and other juices of the body, it may fulfil the rôle

of forming the prosthetic xylose group of nucleo-proteides out of derivatives of glucose.

The enzymes of the animal economy which exercise a hydrolyzing action on the conjugated glycuronic acids are not yet known; possibly bacteria possess this power. On the other hand, ferments occur in plants which are able to split up conjugated glycuronic acid. Neuberg and Neimann observed that emulsin and kefirlactase hydrolyze some conjugated glycuronic acids, especially those with an aromatic conjugate—phenylglycuronic acid, for example—and Hildebrandt (7) has recently found another vegetable ferment—myrosin—which acts on conjugated glycuronic acids.

5. The Origin and Formation of Glycuronic Acid in the Organism.

As already stated, the discoverers of glycuronic acid regarded it as a derivative of grape-sugar, and also accepted its formation from glucose in the animal body. E. Fischer, Piloty and Sundwik (1) have evolved the hypothesis that a union of the pairing body with glucose first occurs, and that subsequently this glucoside is oxidized to conjugated glycuronic acid.



Later, the opinion has been expressed that glycuronic acid is an offspring of protein. This view is most exhaustively urged by Loewi (8), who, whilst regarding the constitution of protein as out of consideration in respect to sugar formation, places it in the first rank among the sources of glycuronic acid. But, according to Mayer (8), Loewi's all-important supposition that a dog at the height of phloridzin diabetes, with otherwise normal food, will be free from glycogen, is controvertible. Mayer has furnished experimental evidence that, in the organism, glycuronic acid can originate from grape-sugar. He showed that rabbits, by being kept from food for ten or twelve days, are practically free from glycogen, and that if camphor is then administered, only an extremely small amount of glycuronic acid is produced; but the administration of grape-sugar at once determines the excretion of an amount of glycuronic acid equal to that which existed before the deprivation of food. Hildebrandt has furnished further evidence of the formation of glycuronic acid from glucose (8). The poisonous thymotinpiperidide becomes harmless when conjugated with glycuronic acid, but the systemic hexoses beyond the glycogen stage, which are being transformed into grape-sugar, are alone capable of effecting this; the non-glycogen type does not possess the power.

Nevertheless, the formation of glycuronic acid out of protein is by no means excluded, nor yet from fat; but as it is difficult to eliminate the direct formation of glycuronic acid or its secondary development from previously existing grape-sugar, Mayer justly contends that the question

of glycuronic acid formation from these substances is practically included in the broader question of the formation of sugar out of fat and protein.

The supposed transference of the glucoside into conjugated glycuronic acid has not, so far, been proved, either chemically or physiologically. Experiments on animals in view of this have been made with α-methylglucoside by Brahm, with β-methylglucoside by Münch, and with β-phenolglucoside by Falck (9). But with the substances named even an indubitable positive result would prove nothing, as these glucosides would probably be first of all split up, and an excretion of glycuronic acid would result from the conjugates thus set free. Mayer's attempts, also, with ferment cleavage of glucose-chloralide and glucose-ethylmercaptal have yielded no decisive result.

6. Where the Conjugation of Glycuronic Acid takes place.

Nothing certain is known as to the place in which the conjugation of glycuronic acid occurs. Embden and Glässner (10) have shown that the production of ether-sulphuric acid may take place in the liver, where, by analogy, Embden also transfers the conjugation of glycuronic acid. Neuberg considers that the evidence in favour of this view is insufficient. Moreover, Pick (10) has shown that the part played by the liver in the physiological synthesis of glycuronic acid cannot be important, since operative injuries affecting the liver function which in a short time lead to death have no influence on the excretion of glycuronic acid. Similarly, æthylendiamine, which produces symptoms resembling those of arsenical poisoning, especially as regards the liver, does not, according to Pohl's experiments, in the least affect the synthesis of phenol-glycuronic acid after the administration of phenol. On the contrary, after administration of amyl alcohol and chloral hydrate, the formation of the equivalent amount of conjugated glycuronic acid is markedly diminished, and in the case of euxanthone is absolutely arrested. On the other hand, Weintraud (10) found after extirpation of the pancreas, as also in the severest cases of diabetes in men and animals, that the formation of glycuronic acid was not altered by the administration of camphor, chloral hydrate, and α-naphthol. It may be inferred from these data that, as is the case in the synthesis of hippuric acid, the formation of glycuronic acid takes place in various parts of the organism.

7. The Behaviour of Free and Conjugated Glycuronic Acid in the Organism.

The researches made by Mayer with free glycuronic acid are important for the explanation of the physiological part played by the acid (8). The fate of the acid and the results produced may be very various. After administration of about 19 grammes of sodium glycuronate to a rabbit, the urine in twelve hours contained a considerably increased amount of oxalic acid—0·0095 to 0·014 gramme—whilst in the normal rabbit only traces of from 0·0005 to 0·0009 gramme were

excreted daily. It is noteworthy that the liver after such large doses contained a considerable amount of oxalic acid (0·05 to 0·08 gramme), the normal liver containing none. Outside the body the still vital liver is also capable of forming oxalic acid out of glycuronic acid. Along with oxaluria, glycosuria often occurs after large doses of unconjugated glycuronic acid. According to Mayer, this is probably indicative of an acid glycosuria, as, although a retrograde change of glycuronic acid into grape-sugar is theoretically possible, no evidence of its occurrence has yet been produced. Külz, however, states that glycuronic acid is a glycogen former (11).

When the amount of glycuronic acid administered is sufficiently large (especially when it is administered subcutaneously), a portion of it escapes oxidation, and appears in the urine, partly in the free and partly in the conjugated state. In the latter case, however, the normal conjugates of glycuronic acid—phenol and indoxyl—are not increased, but the ether sulphates are correspondingly diminished. From this, and from the previously mentioned researches of Falck (9), it is plain that glycuronic acid and sulphuric acid can act vicariously the one for the other, and that when a sufficiency of glycuronic acid is present, the formation of ether-sulphuric acid is considerably suppressed.

The conjugated glycuronic acids, so far as is at present known, undergo no change in the organism. Külz (11) found that phenol-glycuronic acid was excreted unchanged, no damage being caused by the conjugated phenol. Urochloral acid behaved itself similarly.

8. Pathological Excretion of Glycuronic Acid, and its Relation to other Derangements of Carbohydrate Metabolism—Theory of Incomplete Sugar Oxidation.

The chief biological importance of glycuronic acid doubtless lies in its antidotal properties. The conjugation of the acid constitutes a unique chemical means of protecting the organism from the action of certain autogenous poisons. An obvious example of this antidotal function is seen in the normal occurrence of conjugated glycuronic acid in the urine, owing to the formation of small amounts of indoxyl and phenol in the intestinal tract.

Of late years, especially since Mayer's researches directed attention to this point, a number of cases have been recorded in which a considerably increased excretion of glycuronic acid occurred without the introduction of substances which are known to produce it. The explanation of this is clear : the excess of glycuronic acid is due to increased production of the conjugates phenol and indoxyl. Recent researches show that the older view, which assumes an almost universal conjugation of these aromatic substances with sulphuric acid, requires modification ; they also conjugate with glycuronic acid, especially when they are developed in great excess, as in obstruction of the bowels, in ileus, and when collections of pus are formed.

It is more difficult to account for an increase in the excretion of

glycuronic acid when there is no increase in the output of indoxyl and phenol, and in the absence of any known substance introduced from without with which the acid could conjugate. Trustworthy observations of increased excretion of glycuronic acid have been recorded by Mayer (8), occurring in diabetes mellitus, in severe disturbances of the circulation and respiration, in poisoning by carbon monoxide and curare, and also after the administration of very large amounts of grape-sugar to both men and animals. In some instances Mayer observed a considerable decrease in the ether sulphates which corresponded to the excess of glycuronic acid. In one very striking case of cocaine-poisoning in which there was severe dyspnœa, Wohlgemuth (12) found that the total aromatic bodies in the urine were not increased, and that the glycuronic acid was conjugated with a mixture of phenol and cresol. In these cases Mayer assumes that the glycuronic acid formation is the first step, and that it results in a diminished production of ether-sulphuric acid, the condition being due to incomplete oxidation of grape-sugar. The hypothesis advanced is that part of the glucose molecule, after cleavage, passes by way of glycuronic acid into oxalic acid.

In support of the theory of incomplete sugar oxidation Mayer advances the following data, which, at any rate, point to a close relationship between glycosuria and the excretion of glycuronic acid : (1) After the administration of such amounts of glucose as are beyond the assimilation limit, there occurs occasionally an excretion of glycuronic acid, with an equivalent diminution of ether-sulphuric acid. (2) After the administration of chloral hydrate, morphine, and nitrobenzol, sometimes glucose, and at others conjugated glycuronic acid, is present in the urine [Naunyn (12)] ; and G. Hoppe-Seyler (12) found that in some animals *o*-nitrophenylpropiolic acid produced an excretion of glucose, and in others the formation of indoxylglycuronic acid. (3) In diabetes, oxaluria and the excretion of glycuronic acid by no means infrequently accompany each other. (4) An example is forthcoming of progressive cleavage of the glucose molecule within the organism in the transformation of *d*-glycuronic acid into *d*-saccharic acid, thus :

$$COOH—(CH.OH)_4—\mathbf{CH_2OH} \longrightarrow COOH—(CH.OH)_4—\mathbf{COOH},$$

which, both chemically and by formula, strictly corresponds with the transformation of glucose into glycuronic acid, thus :

$$COH—(CH.OH)_4—\mathbf{CH_2OH} \longrightarrow COH—(CH.OH)_4—\mathbf{COOH}.$$

In both instances the reaction consists in a biochemical change of the primary alcohol group $\mathbf{CH_2OH}$ into a carboxyl group, **COOH.**

This hypothesis, accepted by some, has been severely criticised by Bial (3) and Lewin (13) ; but the objections raised do not affect the fundamental principle of the theory. Bial asserts that the irregularity in the amount of glycuronic acid excretion is accounted for by the varying resistance to cleavage displayed by the conjugated acids, by which the mode of their excretion is determined—sometimes in the urine and sometimes in the fæces. This, however, has not been proved. Lewin's

objection that the oxaluria in diabetes causes an increase in protein metabolism, with a resulting increase of aromatic conjugates, especially of phenol and indol, has been disputed on general grounds by Jaffé (13); and Ellinger rejects it under the conditions involved, inasmuch as the mode in which Lewin assumes the development of phenol and indol has no existence.

On the other hand, it is to be clearly understood that Mayer has advanced no proof of the correctness of his theory. It is simply a deduction from facts observed by him, for which an entirely different explanation may possibly be found. This applies especially to all those cases of increased glycuronic acid excretion in which the nature of the conjugate is not known. In many of these cases it is possible that urea may be the conjugate of glycuronic acid, as Neuberg and Neimann (6) have artificially produced ureïdoglycuronic acid, and have found a conjugated glycuronic acid which is in many respects similar. In other instances a conjugate as yet unknown may be present, which would lead to a different interpretation of the conditions under discussion. Equally uncertain is the interpretation of the glycuronic acid excretion after fractures of bones and injuries to muscular tissues, and also after severe contusions. Cadéac and Maignon (13) have made observations on such cases, in which for the most part the excretion of glycuronic acid was accompanied by glycosuria. No statements are forthcoming as to the nature of the glycuronic acid conjugates.

In clinical practice the questions of the highest importance are as to whether the excretion of glycuronic acid is of diagnostic value, and especially whether it is of prognostic signification in diabetes. Mayer has pointed out the possibility that in otherwise healthy individuals an increased output of glycuronic acid without recognisable cause, and in the absence of any increase in aromatic conjugates, may possibly be indicative of the advent of diabetes. The material to hand, however, is insufficient to determine this question; it would be a great mistake to label every patient with occasional increase in glycuronic acid excretion as a future diabetic. Still, there are numerous cases of glycuronic acid excretion which are of a distinctly pathological character, inasmuch as they show clinical features of various kinds; the increased excretion of glycuronic acid, however, does not clinically constitute the original derangement which determines the other deviations from health. The uncertainty of the etiology and the protean form of the appearances at present forbid any recourse to symptomatic treatment; the import of glycuronic acid excretion is being investigated on all sides. See also p. 577 *et seq.* of this volume.

9. The Diagnosis of Glycuronic Acid Excretion.

The recognition of glycuronic acid is founded on the following properties common to almost all conjugated glycuronic acids. The fresh urine is distinctly lævorotatory, but is wanting in reducing power and in the capacity to undergo fermentation. After being boiled with a little 5 per cent. sulphuric acid for from a quarter to three-quarters of an hour,

the lævorotation is changed to dextro-rotation, and coincidently the urine acquires strong reducing powers; a positive reaction is also given with Tollen's orcin test. Instances occur, however, in which reducing power and reaction to the orcin test are present before cleavage. It may also occur that the urine, which is lævorotatory before cleavage, is optically inactive after cleavage, or even remains lævorotatory; this is when the conjugate itself is lævorotatory, or the hydrolysis has not been fully carried out.

LITERATURE.

1. Jaffé: Zur Kennt. der synthet. Vorgänge im Tierkörper. Z. p. C. **2.** 47. 1878.—Schmiedeberg u. Meyer: Ueber Stoffw. produkte nach Kampferfütterung. Ibid. **3.** 422. 1879.—Sundwik: Akad. Abhandl. Helsingfors, 1886.—Fischer u. Piloty: Reduktion der Zuckersäure. B. C. G. **24.** 52. 1891.—Neuberg u. Neimann: Synthese gepaarter Glukuronsäuren. Z. p. C. **44.** 114. 1905.

2. Mayer u. Neuberg: Ueber den Nachweis gepaarter Glukuronsäuren und ihr Vorkommen im Harn. Z. p. C. **29.** 256. 1900.—Mayer: Ueber eine bisher unbekannte reduzierende Substanz im Blute. Ibid. **32.** 518. 1901.—Lépine et Boulud: Sur l'acide glycuron. du sang. C. r. S. B. **133.** 138. 1901; **134.** 398. 1902; **136.** 1037. 1903; **138.** 610. 1904.

3. Lépine: C. r. S. B. **1901.** P. 50.—Bial: Ueber den Befund von gepaarter Glukuronsäure in den norm. Fäzes. Be. P. P. **2.** 528. 1902.—Bial u. Huber: Ueber den Befund von gepaarter Glukuronsäure in den Fäzes nach Mentholdarreichung. Ibid. **2.** 532. 1902.—van Leersum: Gepaarte Glukuronsäuren als Bestandteile der Galle. Ibid. **3.** 522. 1903.—Mayer: Zur Frage der Glukuronsäureaussch. B. k. W. **1903.** Nr. 13, 22. Pp. 292, 514.

4. Bial: Ueber den Befund von gepaarter Glukuronsäure in der Galle. Z. p. C. **45.** 258. 1905.—B. von Fenyvessy: Zur Glukuronsäurefrage. Ar. i. P. **12.** 407. 1903.

5. Orgler u. Neuberg: Ueber Chandroitinschwefelsäure, etc. Z. p. C. **37.** 407. 1903.—Mandel u. Levene: Ueber die Verbreitung von Glukothionsäure im tier. Organismus. Ibid. **45.** 386. 1905.

6. This subject is fully discussed by Neuberg: Physiol. der Glukuronsäure. Er. Ph. **3.** Abt. I. Pp. 433-443.—Also Neuberg u. Neimann: Neue Reaktionen und Derivate der Glukuronsäure. Z. p. C. **44.** 97. 1905.—Jaffé: Ueber das Verhalt. des p-Dimethylaminobenzaldehyds im Stoffw. Ibid. **43.** 374. 1905.—Hildebrandt: Ueber das biol. Verhalt. von Nerol, Geraniol, etc. Be. P. P. **4.** 251. 1904; Ueber das Schicksal einiger zyklischer Terpene und Kampfer im Tierkörper. Z. p. C. **36.** 452. 1902.—Neubauer: Ueber Glukuronsäurepaarung bei Stoffen der Fettreihe. Ar. P. P. **46.** 133. 1901.

7. Daiber: Beitr. zur Kennt. des Auftretens von Indikan und Indoxylschwefelsäure und gepaarter Glukuronsäure im Harne. Sc. W. **33.** Nr. 25. 1895.—Thierfelder: Über Glukuronsäure. Z. p. C. **13.** 275. 1889.—Hildebrandt: Pharmakol. Studien über synthet. Basen. Ibid. **43.** 289. 1904.—Salkowski u. Neuberg: Die Verwandlung von d-Glukuronsäure in l-Xylose. Ibid. **36.** 261. 1902.—Neuberg u. Neimann: See Nr. 1.—Hildebrandt: Zur Frage der glukosid. Struktur gepaarter Glukuronsäuren. Be. P. P. **7.** 438. 1905.

8. Loewi: Ueber den Einfl. des Kampfers auf die Grösse der Zuckeraussch. im Diabetes. Ar. P. P. **47.** 56. 1902.—Mayer: Über Kohlenhydratsäuren. Z. M. **47.** Heft 1, 2. 1902.—Hildebrandt: Ueber einige Synthesen im Tierkörper. Ar. P. P. **44.** 278. 1900.

9. Brahm: Ueber das Chinosal und die Bildung gepaarter Glukuronsäuren. Z. p. C. **28.** 438. 1899.—Münch: Ueber das Verhalten einiger künstlicher Hexosen im Tierkörper. Ibid. **29.** 493.—Falck: Ueber das Verhalt. einiger Glukoside sowie über die Entstehung gepaarter Glukuronsäuren im Tierkörper. Mü. m. W. **1902.** Nr. 36. P. 1489.—Mayer: see Nr. 8.—Mayer: Ueber das Verhalt. des Glukoseäthylmerkaptals im Organismus.—Salkowski Festschr. **1904.** P. 255.

10. Embden u. Glässner: Ueber den Ort der Aetherschwefelsäurebild. im Tierkörper. Be. P. P. **1.** 310. 1901.—Embden: Ueber die Bild. gepaarter Glukuronsäuren in der Leber. Ibid. **2.** 591. 1902.—Mayer: See Nr. 2, 3.—Pick: Ueber die Beziehungen der Leber zum Kohlenhydratstoffw. Ar. P. P. **33.** 305. 1894.—Weintraud, cit. by Naunyn: Diabetes mellitus. P. 155.—Pohl: Ueber Synthesenhemmung durch Diamine. Ar. P. P. **41.** 97. 1898.

11. Külz: Festschrift für Ludwig. 1891.—Külz: Zur Kenntnis der synthet. Vorgänge im tier. Organismus. Ar. P. M. **30.** 484. 1883; and Z. B. **20.** 157. 1884.

12. Wohlgemuth: Ueber Glukuronsäurebild. beim Menschen. B. k. W. **1904.** Salkowski Number. P. 1084; and Z. M. **56.** 407. 1905—Hoppe-Seyler: Ueber das phys. Verhalt. der o-Nitrophenylpropiolsäure. Z. p. C. **7.** 178. 1883.—Naunyn: Diabetes mellitus. Pp. 28-32. 1898.

13. Lewin: Ueber die Bildung von Phenol und Indoxyl im intermed. Stoffw. und deren Beziehung zur Glukuronsäureaussch. Be. P. P. **1.** 472. 1902.—Jaffé: Die Indikanurie und ihre pathol. Bedeutung. D. K. **11.** 214. 1903.—Ellinger: Indolbildung und Indikanaussch. beim hungernden Kaninchen. Z. p. C. **39.** 44. 1903.—Cadéac u. Maignon: C. r. S. B. **134.** 1001 and 1443. 1903.

Besides ordinary diabetes, lævulosuria, pentosuria, and glycuronic acid excretion, we know of no anomalies of carbohydrate metabolism in which monosaccharides are excreted. Possibly galactose constitutes an exception; but as galactosuria stands in such close relation to milk-sugar excretion, and is dependent upon it, it will be best described along with lactosuria. We have just as little certain knowledge concerning anomalies of carbohydrate metabolism in which the higher polysaccharides appear in the urine. On the other hand, carbohydrate urines exist in which disaccharides appear; these, in part, have been well studied.

IV.—LACTOSURIA.

1. Spontaneous Excretion of Milk-sugar.

This only occurs in females, and it stands in the closest relationship with the changes in metabolism during gestation. Blot (1) was the first to observe the presence of a peculiar carbohydrate in the urine of parturient women; the nature of the carbohydrate was subsequently determined by Hofmeister (2) and Kaltenbach (3). Claude Bernard had previously expressed the opinion that the lactosuria was due to irregularities of lactation; this view was more fully expressed by Fehling and Hofmeister.

Lactosuria is usually first observed a few days after delivery; occasionally, however, it occurs during the latter days of gestation [Ney (4), Lemaire (5), Porcher (6)]. The last-named observer made a number of careful investigations concerning the excretion of milk-sugar by domestic animals. Leblanc and Guillot (7) have shown that in the cow, and to some extent in the mare, lactosuria occurs before the commencement of the puerperium, and that after the establishment of lactation the excretion of milk-sugar diminishes and finally ceases. Ney found milk-sugar in the urine of 77·7 per cent. of parturient women, but only in 16 per cent. of pregnant women. According to Naunyn, the amount of milk-sugar

excreted by parturient women equals from 2 to 3 per cent. Porcher (8) gives it as 4 per cent. McCann (9) puts the average at 0·35 per cent. for the fourth and fifth days of the puerperium.

This gestation-lactosuria is a very frequent accompaniment of the gravid state, but it is not a pathological phenomenon ; the conditions which lead to its occurrence are easily recognisable. Numerous writers have unanimously decided that milk-sugar introduced into the system without reaching the intestines is almost entirely excreted in the urine, as neither the tissues nor the blood possess the power of hydrolyzing it. In all kinds of lacteal engorgement, lactose, as a secretion of the breasts, escapes from the milk-ducts into the general circulation, and thence passes into the urine. Camerer and Söldner (10) found that the colostrum contains a considerable amount of lactose (1·73 to 4·07 per cent.), so that by absorption of plentifully formed colostrum milk-sugar may be excreted before labour ; the much commoner lactosuria during the early days of childbirth is accounted for by insufficient withdrawal of the milk by the infant. In fact, when suckling is interrupted, the amount of milk-sugar in the mother's urine is often materially increased ; and the lactosuria in women who suckle their children is less than in those who do not. According to Ney, milk-sugar is constantly present long after confinement in the urine of women whose secretion of milk considerably exceeds the infant's demand. Pavy (11) states that after many months' suckling, if the infant is suddenly weaned, lactosuria occurs.

2. Alimentary Lactosuria.

Artificial lactosuria is easily produced, on account of the low assimilation limit for milk-sugar ; for the present purpose, however, only those cases of milk-sugar excretion are of interest which partake of the nature of anomalous metabolism. Méhu (12) was the first to observe that patients, after prolonged and copious use of milk, excrete lactose ; and Gróss (13) made the first trustworthy statements concerning the presence of milk-sugar in the urine of breast-nourished infants with gastro-intestinal diseases. Langstein and Steinitz have recently undertaken more exact researches on this condition (14) (see p. 56). In fourteen cases of severe nutritional disturbances occasioned by gastro-intestinal diseases the presence of milk-sugar in the suckling infants' urine was revealed by its characteristic osazon. So far, the amount of the excreted sugar has not been determined, but it was ascertained that in five cases it was accompanied by a second carbohydrate—galactose. Lactosazon may be distinguished from galactoazon and glucosazon by its ready solubility in hot water.

In gravid lactosuria the milk-sugar, without reaching the bowels, passes into the circulation ; it is otherwise with the lactose excretion of the suckling, in whom it is absorbed from the digestive tract. By special researches, Langstein and Steinitz have proved that this excretion is not due to failure of the normal enzyme, lactase, which is especially produced in the jejunum, but to an unknown derangement of the activity of the

lactase, which renders it incapable of splitting up the whole of the milk-sugar, the remainder being absorbed unchanged. On account of the absence of a hydrolyzing enzyme in the systemic juices, this remainder of unaltered milk-sugar is excreted as such. From the portion which is split up in the bowel, the resulting easily assimilable glucose is utilized by the organism ; the other component, galactose, on account of its much lower assimilation limit, partly escapes by the kidneys. Thus it is that lactosuria is accompanied by the excretion of galactose. This explanation is partly founded on the researches on animals made by Luzzatto (15), who, after feeding a dog copiously with milk-sugar, was able, by interposing special conditions, to procure the excretion of the galactose component alone.

Parturient women are characteristically affected by milk-sugar administered by the mouth ; thus, after taking 100 grammes each of lactose eleven out of thirteen excreted appreciable amounts in the urine ; whilst with non-pregnant women the same treatment only exceptionally produced alimentary lactosuria [Zülzer (16)]. C. von Noorden (17) describes like results with only 50 grammes of lactose. Indicative of the close relation that exists between the gravid state and the excretion of milk-sugar are some further observations of von Noorden and Zülzer, which tend to show that during gestation lactose can be directly elicited from the organism by other easily assimilable carbohydrates. Magnus-Levy puts a different construction on this occurrence. Hess made similar observations to those of von Noorden on parturient women. With five out of sixteen parturient women it was found, after the administration of 150 grammes of grape-sugar, that lactose appeared in the urine ; a like reaction occurred in women who had aborted or had miscarried. Therefore, before the secretion of milk occurs in the mammary glands, it appears that there is a distinct tendency on the part of the organism to secrete milk-sugar. In a certain sense it is true that puerperal lactosuria may be regarded as an auto-alimentary lactosuria ; but from the real alimentary lactosuria it may be easily differentiated by the extreme readiness with which it can be induced. The difference is very obvious when the amount of milk-sugar in women's milk is considered ; according to Heubner, it averages from 5 to 7 per cent., and colostrum only contains from 2 to 4 per cent. In relation to this, von Noorden has suggested the hypothesis that during lactation the organism, in a certain degree, has lost the capacity to split up milk-sugar, an arrangement which is in favour of the infant.

For a long time it has been supposed that the formation of milk is due to a stimulation which emanates from the developing ovum, and Hildebrandt (18) has endeavoured chemically to explain this view. Possibly it is not too daring to assume that among the reactions which occur in the woman's organism after conception may be numbered the production of an antiferment to lactase ; or, following Weinland's interesting researches, to assume the opposite occurrence—the inhibition of an existing enzyme.

3. The Diagnosis of Lactosuria.

The occurrence of lactosuria is assumed when the urine is found to possess reducing properties and optical activity (dextro-rotation), but is incapable of fermenting with ordinary yeast within twelve hours. After the urine is boiled for about an hour, with 2 to 5 per cent. of sulphuric acid, and neutralized, the milk-sugar is hydrolyzed into galactose and grape-sugar, so that the optical activity of the resulting solution is increased, and it is now capable of undergoing fermentation. The osazon of milk-sugar is also characteristic. Differing from the corresponding combinations of the ordinary hexoses, it is soluble in hot water ; its melting-point is 198° C. to 200° C. It is easily distinguished from the somewhat similar maltosazone by its want of optical activity when dissolved in a solution of alcohol and pyridine.

LITERATURE.

1. Blot : Ga. H. **1856.** Nr. 121 ; and C. r. S. B. **43.** 666.
2. Hofmeister : Ueber Laktosurie. Z. p. C. **1.** 101. 1877.
3. Kaltenbach : Ueber Laktosurie der Wöchnerinnen. Z. p. C. **2.** 360. 1878.
4. Ney : Ueber das Vorkom. von Zucker im Harne des Schwangeren, Gebärenden und Wöchnerinnen. Ar. Gy. **35.** 239. 1889.
5. Lemaire : Ueber das Vorkom. von Milchzucker im Harn bei Wöchnerinnen. Z. p. C. **21.** 442. 1895.
6. Porcher : De la lactosurie chez les femelles au moment du part et en état de lactation. B. M. v. **1902.** 24 Juillet and 13 Nov.
7. Leblanc et Guillot : C. r. S. B. **34.** 585.
8. Porcher : Contrib. à l'étude de la lactosurie. B. M. v. **1903.** 30 Sept.
9. McCann : Lactosuria. L. **1897.** I. 1174.
10. Camerer u. Söldner : Anal. der Frauenmilch. Z. B. **33.** 43. 1896.
11. Pavy : Note on Lactosuria. L. **1897.** I. 1075.
12. Méhu : Jo. P. (5). **16.** 145. 1887.
13. Gróss : Über Glukosurie im Säuglingsalter, etc. Ja. K. **34.** 83. 1892.
14. Langstein u. Steinitz : Laktase und Zuckeraussch. bei magendarmkranken Säuglingen. Be. P. P. **7.** 575. 1906.
15. Luzzatto : Über das Verhalten von Laktose und Galaktose bei Hunden. Ar. P. P. **52.** 106. 1905.
16. Zülzer : Ueber aliment. Glukosurie. C. m. W. **1894.** 485.
17. von Noorden : Ar. A. P. **1893.** 385.
18. Hildebrandt : Zur Lehre von der Milchbildung. Be. P. P. **5.** 463. 1904.
19. Neuberg : Reinigung der Osazone und Bestimmung ihrer optischen Drehungsricht. B. C. G. **32.** 3384. 1899.

V.—MALTOSURIA.

The occurrence of maltose among the products of human metabolism is by no means astonishing, seeing that it plays an important rôle as an intermediate product in the conversion of glycogen and starch into sugar, and that is is also closely allied to glucose. Notwithstanding this, genuine cases of true maltosuria are rarely met with.

Lépine and Boulud (1) occasionally found small quantities of maltose along with glucose in cases of diabetes. Charrin and Brocard (2) state that they found maltose in the urine of puerperal women; more reliable are the cases described by C. Nobel (3), von Ackeren (4), and Rosenheim and Flatow (5). These authors observed maltosuria in diseases of the pancreas; in interstitial pancreatitis Rosenheim and Flatow found from 0·1 to 0·5 per cent. of maltose. The results obtained by Lépine and Boulud (6) after complete removal of the pancreas in dogs show the part played by it in many forms of maltosuria; in a litre of the urine 1·95 to 3·06 grammes of maltose were found, along with about 50 to 90 grammes of grape-sugar. The same authors (7) found that a diabetic woman aged forty years excreted 1·93 to 2·78 per cent. of maltose, with 4 to 6 per cent. of glucose. Lépine also previously observed a case of slight maltosuria.

These statements concerning maltosuria are founded on the differences between the polarimetric and the titration methods of estimating the amount of sugar in the urine. The rotating power of maltose is about two and a half times greater than that of grape-sugar, whilst its reducing power is only about two-thirds of it. It is to be borne in mind, however, that pentose, fructose, lactose, glycuronic acid combinations, as well as other optically active substances such as β-oxybutyric acid and amino-acids, may occasion considerable differences between the reducing and the optical properties of urine, and thus introduce sources of error which are difficult to avoid; on this account, many of the published reports of the excretion of maltose are not beyond suspicion. Satisfactory proof is only obtained by means of complete fermentation, and by the production of the characteristic maltosazon, which, though resembling lactosazon as regards solubility, is easily distinguished by its optical powers. Obviously the difficulty of determining the occurrence of maltose in urine is proportional to the amount that is present; an absolutely certain diagnosis is only possible when the quantity of maltose is sufficiently large to eliminate experimental error.

The following well-marked case of maltosuria, investigated by Magnus-Levy in the Strasburg Clinic, was privately communicated by him. The urine yielded a considerable excess of rotation when compared with its reducing power. After inversion with dilute acid, by which each molecule of maltose was converted into two molecules of grape-sugar, the rotation diminished and the reduction increased, so that the polarimetric and the titration methods afforded concordant results. Calculations founded on the determinations thus obtained showed that 1·5 per cent. of maltose and about 2 per cent. of glucose were present. The evidence thus obtained was corroborated by the urine undergoing complete fermentation, with synchronous loss of optical activity and of reducing power. This condition was observed on two consecutive days. The case is remarkable on account of the large amount of maltose excreted, which exceeds all previous records; for this reason (although no osazon was obtained) the observation is more reliable than other records.

LITERATURE.

1. Lépine et Boulud : C. r. S. B. **126.** 610.
2. Charrin et Brocard : Die Glukosurie der Schwangerschaft. Ibid. **50.** 1077. 1898.
3. Nobel : Ein Fall von Fettstuhlgang mit gleichzeitiger Glukosurie. Ar. M. **43.** 285. 1888.
4. Ackeren : Ueber Zuckeraussch. bei Pankreaserkrankungen. B. k. W. **1889.** P. 293.
5. Rosenheim u. Flatow : Chron. interstitieller Pankreatitis. B. k. W. **1898.** 317.
6. Lepiné et Boulud : Maltosurie chez certaines diabétiques. C. r. S. B. **132.** 610. 1901.

VI.—THE EXCRETION OF CANE-SUGAR AND OF ISOMALTOSE.

Under ordinary dietetic conditions, alimentary saccharosuria only exceptionally occurs, on account of the high assimilation limit of cane-sugar. Spontaneous excretion of cane-sugar has never been actually proved. Seeing that lævulose occurs in the organism without being introduced along with food, the *a priori* possibility of a synthetic formation of cane-sugar in the body analogous to that which occurs in plants cannot be denied ; indeed, according to Lépine and Boulud (1), it occasionally occurs in the blood of dogs, especially after extirpation of the pancreas.

By condensation of grape-sugar, E. Fischer obtained the disaccharide isomaltose, but its occurrence under natural conditions has not yet been determined with certainty. According to Baisch (2), Lemaire (3), Reinbold (4), Porcher (5), and Pavy and Siau (6), isomaltose occurs in normal urine ; and, according to Rosin and Alfthan (7), in diabetic urine also. Salkowski (8) and Mayer (9) believe that in many instances errors of interpretation have been made, especially in relation to glycuronic acid. No instance of pathological isomaltosuria has yet been recorded. Cremer (10) alludes to the possibility of an alimentary isomaltosuria.

LITERATURE.

1. Lépine et Boulud : Sur les sucres du sang. C. r. S. B. **133.** 138. 1901 ; **134.** 398. 1902.
2. Baisch : Ueber die Natur der Kohlenhydrate des Harns. Z. p. C. **20.** 249. 1894.
3. Lemaire : Ueber das Vorkom. von Milchzucker im Harn bei Wöchnerinnen. Z. p. C. **21.** 446. 1895.
4. Reinbold : Ueber die Verwendbarkeit der Benzoylierung zur quantit. Bestim. der Kohlenhydr. im Harn. Ar. P. M. **91.** 35. 1902.
5. Porcher : C. Z. **26.** 576.
6. Pavy and Siau : Nature of Sugar present in Normal Blood, Urine, and Muscle. J. P. **26.** 282. 1901.
7. Rosin u. von Alfthan : Ueber die quant. Verhält. der Kohlenhydrate im diabet. Harn. D. m. W. **26.** 497. 1900 ; C. Z. **24.** 238.
8. Salkowski : Ueber das diabet. Ferment der Leber. Ar. P. M. **56.** 351. 1894.
9. Mayer : Ueber eine bisher unbekannte reduzierende Substanz des Blutes. Z. p. C. **32.** 518. 1901.
10. Cremer : Ueber das Verhalten einiger Zuckerarten im tier. Organismus. Z. B. **29.** 513. 1892.

VII.—INOSITURIA.

For many years it has been known that inosite does not belong to the carbohydrate group, but that it is a member of the aromatic series, being a hexaoxy-hexahydrobenzol—$C_6H_6(OH)_6$ (hexahydroxymethylene). The original idea, founded on the isomerism of inosite with grape-sugar, was to regard inosituria as an anomaly of carbohydrate metabolism. This lacks chemical foundation, but the part which inosite plays in natural phenomena, its diffusion and its frequent occurrence in animals and plants alongside sugar, indicate interchangeable relations in metabolism. A chemical relation of inosite to the hexoses has frequently been assumed, by which, under certain conditions, the open, acyclic chain of sugar, by intramolecular aldol-condensation, passes over into the cyclic form of the isomer inosite :

$$\begin{array}{l} CH.OH—CH.OH—COH \\ \quad | \\ CH.OH—CH.OH—CH_2OH \end{array} \longrightarrow \begin{array}{l} CH.OH—CH.OH—CH.OH. \\ \quad | \qquad\qquad | \\ CH.OH—CH.OH—CH.OH \end{array}$$

In small amount inosite enters into the composition of almost all animal tissues, and, so far as is known, it only occurs in the optically inactive form of meso-inosite (corresponding to meso-tartaric acid). In the vegetable world optically active forms of inosite also occur.

On account of the widespread occurrence of inosite, small amounts are frequently found in the urine [Hoppe-Seyler (1)]. Nothing is known as to the extent of this physiological inosituria. According to Külz, however, it is very doubtful if normal urine contains inosite ; it only appears after copious intake of water. This type of inosituria, found by Strauss (3) and Külz (4) in diabetes insipidus, after the ingestion of large amounts of water, in granular kidney, etc., appears to be simply caused by the flushing of inosite out of the organism.

As regards spontaneous chronic inosituria, there is an old statement by Vohl (5) of a case of diabetes in which glycosuria was replaced by inosituria ; the daily output of inosite reached 18 to 20 grammes. On the other hand, the administration of inosite did not increase a glycosuria [Külz]. The statements of Gallois (6) and of Külz (2) point to a relation between diabetes and inosituria ; the latter was observed in cases of glycosuria associated with albuminuria.

Alimentary inosituria can be produced in human beings by the administration of inosite, but it is only of a mild type ; after giving from 30 to 50 grammes, Külz found only 0·75 to 0·95 per cent. of it in the urine. Inosite, therefore, belongs to those substances which are capable of being almost entirely destroyed in the system, so that the small amounts of inosite in food are without influence on cases either of glycosuria or of inosituria.

The clinical significance of the excretion of inosite is quite unknown. There are some grounds for believing that in many respects inosite resembles extractives, and that the inosituria of diabetics is also due to

copious flushing out of the tissues determined by some unknown stimulus.

The recognition of inosite is accomplished by testing the isolated substance with the reactions of Scherer, Gallois, Seidel, and Maquenne.

LITERATURE.

1. Hoppe-Seyler, cited by Blumenthal: Path. des Harns. 1903. P. 165.
2. Külz: Ueber das Auftreten von Inosit im Harn gesunder Individuen. Sit. M. 1875. P. 78, and 1876. P. 70.
3. Strauss: Diss. Tübingen, 1864.
4. Külz: Path. und Ther. des Diabetes. Sit. M. 1874 and 1875. Bd. I. P. 171; Bd. II. P. 29. Z. a. C. 16. 135.
5. Vohl: Ueber das Auftreten des Inosits im Harn. A. p. H. 2. 410. 1858; and B. C. G. 9. 984. 1876.
6. Gallois: De l'inositurie. 1864; and Z. a. C. 4. 264.

CHAPTER V

DISEASES OF THE SKIN

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The pathology of skin disease has always embraced a much wider field than the mere study of the local lesion. An intimate connection between the skin and the body as a whole was recognised long ago, for the frequent occurrence of a general erythema after the ingestion of some particular food or drug could not fail to attract notice. In fact, the skin was supposed to have the attribute of "drawing out" certain diseases, a property much traded upon in the older systems of therapeutic art; while—in England, at least—the fear of a cutaneous eruption "striking inwards" is, in the popular mind, by no means extinct.

Moreover, the acute exanthems and small-pox—the dread scourge of the Middle Ages—were only too well known by their constitutional effects. Small wonder, then, if the physicians of former days sometimes shot far beyond the mark, and saw in the itch ("psora") a cause for every malady. Our modern ideas can still provide many a parallel to the older views, and this will, to some extent, affect the scope of our work, since here, rather more, perhaps, than in other departments of the pathology of metabolism, we shall not only have to consider and discuss the position of our exact knowledge, but must include many clinical facts, hypotheses, and theories.

Unfortunately, the sum total of available scientific information forms as yet too slender an array to oust from their ill-gotten eminence the several tendencies, diatheses, and -isms that now reign supreme in dermatology.

I.—INFLUENCE OF SKIN DISEASES ON NUTRITION AND EXCHANGE OF ENERGY.

1. General Effects—Fever.

It is a daily experience that skin diseases can affect the general nutrition. This is seen if the health of the patient is seriously interfered with by pain or fever; the appetite is lost, and the intake is consequently

diminished. On the other hand, the output may be increased by broken sleep, by the irritation of the affected skin, by scratching, or restlessness. A progressive wasting, which is not easily arrested, then results.

Pyrexia does not play any very considerable part in the pathology of skin diseases, for the temperature remains practically normal in most of them, although fever may be met with in many of the erythematous and vesicular eruptions, pemphigus, dermatitis herpetiformis, and particularly in severe burns, when there is a fairly regular rise of temperature [M. Wilms (1)]. Syphilis is quite commonly associated with a raised temperature during the eruptive stage.

In gonorrhœa some French authors [Rouanet, Noguès (2)] have made numerous observations, and in uncomplicated cases have found the temperature constantly normal. We have, however, frequently met with irregularly raised temperatures even in uncomplicated cases of gonorrhœa. Every clinical observer is familiar with the converse, that processes implying profound malnutrition—*e.g.*, the cachexia of phthisis and carcinoma—are reflected in the state of the skin, which loses something of its bulk, feels thin and dry, and shrivels up. Owing to the loss of subcutaneous fat, it becomes more easily pinched up from the underlying structures. Heller (3) has carefully worked at this subject, and finds that in many severe diseases, such as typhus, icterus gravis, enteric fever, pneumonia, erysipelas, scarlet fever, measles, rheumatic fever, and even in febrile epididymitis, an arrested growth of the nails takes place, as shown by the appearance of a transverse furrow, just as the horns of a cow are sometimes marked with a ring for each calving.

It is worth noting that in burns subnormal temperatures have been described directly after the accident [Bedard, Th. Billroth (4)]. As yet no definite explanation of this fact has been given. Perhaps it is due to some reflex effect on the temperature centre.

Linser's recent work on the subject of heat regulation (240) is of great value, showing, as it does, a marked relation between increased heat loss and increased katabolism. In three cases of universal skin disease—eczema, psoriasis, and erythrodermia exfoliativa—he demonstrated that the difference between the surface and rectal temperature was only 1° C., instead of the customary 3° to 3½° C. of health. This alteration, he considers, is due to the dilatation of the capillaries of the skin, and is responsible for an increased heat loss. Continuing his researches by an estimation of the nitrogen exchange, he found in the case of psoriasis and erythrodermia exfoliativa (complicated by pseudo-leuchæmia) that the albumin destruction was markedly decreased by exposure to a higher temperature. In the tables quoted the first five days were spent in each case in a room kept at a temperature of 15° C. to 18° C., with the patients in bed, and sufficiently covered not to complain of the cold. During the following three days the heat of the room was raised to 26° C. to 30° C. The diminished heat loss so obtained probably accounts for the altered rate of nitrogen exchange.

Psoriasis Vulgaris.

Date.	Intake.		Output.				External Temperature.
	Body-weight.	Food Nitrogen.	Urine Nitrogen.	Fæces Nitrogen.	Total Nitrogen.	Uric Acid.	
	Kg.	Gm.	Gm.	Gm.	Gm.	Gm.	
20	61·2 per diem 3,100 cal. =50 cal. per kg.	25·3 per diem 3,100 cal. =50 cal. per kg.	20·5	11·2 =2·2 per diem	22·7	0·68	16° C.–18° C.
21			21·6		23·8	0·81	
22			23·9		26·1	0·81	
23			23·6		25·8	0·73	
24	60·8		23·0		25·2	0·73	
25	60·8	25·3	20·1	8·1 =2·7 per diem	22·8	0·97	26° C.–30° C.
26	—	—	21·5		24·2	0·97	
27	—	—	21·8		24·5	0·97	
28	61·3	25·3	23·2	2·6	25·8	1·34 (coffee)	18° C.–20° C.

Erythrodermia Exfoliativa—Pseudo-leuchæmia.

Date.	Intake.		Output.				External Temperature.
	Body-weight.	Food Nitrogen.	Urine Nitrogen.	Fæces Nitrogen.	Total Nitrogen.	Uric Acid.	
	Kg.	Gm.	Gm.	Gm.	Gm.	Gm.	
20	83·0 per diem 3,850 cal. =47 cal. per kg.	27·9 per diem 3,850 cal. =47 cal. per kg.	24·8	11·8 =2·4 per diem	27·2	1·02	16° C.–18° C.
21			24·5		26·9	1·14	
22			24·9		27·3	1·14	
23			25·3		27·7	0·97	
24	82·4		25·6		28·0	0·97	
25	82·4	27·9	23·1	8·9 =3·0 per diem	26·1	1·28	26° C.–30° C.
26	—	—	22·4		25·4	1·28	
27	—	—	23·3		26·3	1·28	
28	82·9	27·9	25·9	2·9	28·8	1·51 (coffee)	18° C.–20° C.

2. Specific Effects.

Whether, in addition to the effects of skin diseases upon the nutrition associated with itching and fever, which are quite easily observed, there are also effects upon the extent of the oxidation process and exchange of energy, is a point of the greatest interest. It is well known that in animals the consumption of energy depends to a great extent upon the exposed surface. It is important to know whether in extensive disease of the skin this general biological law holds good. There have been very few investigations made on the subject. The first research upon

respiratory exchange was made nine years ago by Stüve (5), under von Noorden's direction, in a patient with widespread psoriasis. The result showed an absolutely normal rate of O intake and CO_2 output. Tendlau (6) recently found the same result in a case of universal atrophy of the skin with anhidrosis ; and Ludwig Mayer recorded similar figures in a case of sclerodermia in von Noorden's clinic. The value of the results arrived at by Quinquaud and Leredde (7) in mycosis fungoides cannot be correctly estimated, for nothing is said as to the methods adopted. At any rate, all these investigations should be regarded as inconclusive. The hitherto scanty examinations made have all been on subjects kept absolutely at rest. It may well be that by setting up a more vigorous action of the skin, and by muscular exertion, differences in the heat loss and at the same time an indirect effect upon heat production and exchange of energy might be discovered. Some observations made by Tendlau in the case of atrophy of the skin point this way.

3. Vascular Glands and the Skin.

There is no doubt that certain disturbances of metabolism occur which sometimes sympathetically affect the skin, and at other times are associated with changes in the exchange of energy. We see this in old age, where the heat exchange of the body falls in a marked degree, and the suggestion has been made that the gradual decline of the whole oxidation process in old age may be the direct consequence of the atrophic changes in the skin, though in the meantime this connection seems most improbable. On the contrary, it may rather be that the withering and atrophy of the skin in old age are only a local expression of the failing power of repair in the protoplasm generally.

To this category belong, too, those diseases in particular which, in exact contrast to one another, depend upon the state of the thyroid gland and involve the skin, such as myxœdema with diminished, and Basedow's disease with increased, energy exchange.

The close connection between the condition and functions of the thyroid gland—perhaps also of the other vascular glands—and the degree of total oxidation in the body make what is known of the relations of these organs to skin disease a very suitable subject for discussion.

(*a*) *Clinical Observations.*

In myxœdema, a disease associated with marked lowering of the thermogenetic processes of the body, an œdema-like myxomatous infiltration of the skin is seen. It is remarkable that in other diseases also —Basedow's disease, sclerodermia, etc.—changes in the skin similar to myxœdema have been described.

There is, however, no anatomical proof of the analogy of these changes with myxœdema, nor in such investigations as have been made has the decreased heat production so characteristic of myxœdema been demonstrated. It may be assumed that in many of these cases of so-called combination with myxœdema the similarity extends no further than to the external appearance. While in myxœdema the thyroid origin of

the disease has been proved beyond all doubt, the connection of other skin diseases with disturbance of the thyroid function has been suggested only hypothetically. In sclerodermia, above all, this has often been the case. The idea was supported by the frequent coincidence of Basedow's disease and sclerodermia (9 and 10), or even by the atrophic changes found in sections of the thyroid in sclerodermia (11). Moreover, the alleged benefits of thyroid treatment in this disease seem to bespeak some connection ; but there is not yet enough known to settle the question (12).

We ourselves in a case of sclerodermia with typical changes in one leg, the skin of which was extensively shrunken, could discover nothing to support the idea of thyroid disease in the rate of O intake and CO_2 output. The patient, a small, well-developed man, inspired 3·68 c.c. O and expired 2·74 c.c. CO_2 per minute and kilogramme (Zuntz-Geppert method).

Moreover, a recent suggestion made by Volhard (13), that sclerodermia stands in somewhat the same relation to acromegaly as myxœdema to Basedow's disease, was not supported by these estimations. According to this theory, since the heat production is often increased in acromegaly [Magnus-Levy, Salomon (8)], one would expect a decreased O intake in sclerodermia. At any rate, further experiments upon the respiratory exchange are needed.

Apart from sclerodermia, post-mortem observations have established a connection between congenital ichthyosis and changes in the thyroid gland [Windfield and van Cott (14)] ; while Weiss (15) has put forward a similar hypothesis for the so-called adiposis dolorosa.

The often-observed connection between Basedow's disease and skin changes—such as pigmentation, leucodermia, atrophy of the nails, and partial or universal alopecia—while not directly traceable to any change in the substance of the thyroid gland, are at any rate very remarkable.

Moreover, there are some skin diseases, the appearance of pruriginous eruptions and acne rosacea at the menopause, which have been attributed to changes in the organs of generation.

(*b*) *Therapeutic Views.*

Starting from the disappearance of the skin changes in myxœdema under thyroid treatment, Byrom Bramwell (16) has sought to introduce this treatment for skin diseases in general, but his lead has not been followed to any extent. The reports read very differently. The recommendations of Gordon Dill, Zum Busch (17), and others, are directly contradictory to the dogmatic opinions of Thibierge, Abraham, Zarubin, Scatchard, and others (18). The diseases in which thyroid treatment is recommended are especially psoriasis, ichthyosis, lichen ruber, and sclerodermia. This much only is certain, that so experienced an observer as Ewald (19) was able in many cases to report undoubted results. As to the mode of action we have as yet no explanation.

Saalfeld and Sottas (20) have seen some results from organo-therapy in the cure of skin eruptions caused by the climacteric and castration by the administration of ovarian substance (" ovarin " tablets).

II.—INFLUENCE OF DERMATOSES ON PERSPIRATION.

The great part played by the skin in the evaporation of water and the regulation of the body temperature makes it appear a very important question whether in many dermatoses the insensible perspiration is affected as well as the sensible. Certainly, the vital importance of insensible perspiration has been long overestimated.

1. Experimental Evidence.

(*a*) *In Animals.*

It has been found in animals, especially rabbits, that the closing of the pores of the skin by impermeable media like varnish, oil, lanoline, vaseline, etc., was followed by loss of health and death. While the cause of death was originally attributed to retention of the skin secretions—*e.g.*, water, CO_2, ammonia, and volatile aromatic substances [Edenbuizen (21), Lassar (22)], and the resorption of substances put on the skin—Krieger, Laschkewitsch, Lomikowsky, Winternitz, and others (23), have pointed out that the ill-effects seen in the animals experimented on were in reality due to increased heat loss and diminished intrinsic heat.

Lassar's view cannot yet be entirely rejected, and the condition still lacks a complete explanation ; for in some thorough investigations on rabbits, Babák (24) has quite recently shown that animals smeared with absolutely inactive media—*e.g.*, gelatin—can maintain for a week a heat loss increased by 140 per cent. without suffering the least injury. The increased heat loss was balanced by increased heat production, and so the body temperature was kept constant. Babák suggested that the fall of the body temperature after smearing with oil, varnish, etc., might be due to a defective heat production resulting from some toxic process.

Ricciardi (268) claims to have produced in animals various toxic changes in the blood and tissues by varnishing part only of the skin. He states that by applying a varnish consisting of indiarubber in benzene, covered with a layer of collodion, to varying extents of the skin, the death of the animal may be delayed for different periods, demonstrating that as a smaller surface is treated with the varnish, the longer the animal survives, while if the total surface is varnished death ensues rapidly, with the pathological appearances of acute toxæmia. In the less rapidly fatal cases the internal organs—kidneys, lungs, and liver—are found to have developed the signs of (non-microbic) parenchymatous inflammation.

Not only did he find these histological changes in the viscera, but he also carefully investigated the blood conditions. The number of corpuscles, percentage of hæmoglobin, and the spectroscopic appearance, were practically normal ; there was a raising of the freezing-point depend-

ing on an increase of CO_2 in the blood, and the isotony was increased (Mosso-Viola method); while the agglutinating and hæmolytic power of the serum was reduced to nil.

All these effects Ricciardi attributes to an interference with the emunctory processes of the skin, which he considers are capable, even if only partially abolished, of producing these evidences of toxic absorption. He does not, however, adduce any proof that the varnishing media remain entirely unabsorbed and innocuous, but mentions one fact, namely, a complete loss of hair in the unvarnished skin immediately surrounding the part treated, which suggests that an active absorption rather than a general non-excretion may play some part in causing the phenomena he relates.

(*b*) *In Man.*

The story has often been quoted of the boy who at the coronation of Pope Leo X. was to have appeared as an angel, and was for that purpose gilded over the whole of his body, but on the night before the ceremony suddenly died.

An accurate estimate of the pathological importance of checked sweating in man has been arrived at by Senator (25), who showed that in most cases varnishing of the skin does no harm, much less has it a fatal effect. It has to be taken into consideration, however, that the subjects of Senator's experiments were kept in bed under the most uniform conditions. Pathological experience shows that, under certain conditions, disturbances may be set up by checking the water evaporation [*cf.* Levy-Dorn (26)]. With reference to these clinical observations, it should be mentioned that it is not yet certain whether the evaporation of water through the skin takes place via the sweat glands simply, or through some other parts of the skin as well. At any rate, the "insensible perspiration" of the older authors proceeds parallel with sweat secretion, and we are agreed as to the impossibility of separating them one from the other in dealing with the subject of "perspiration."

No information is available on the question of CO_2 evaporation generally.

2. Clinical Facts.

The following clinical facts have been observed:

Very deficient or absent sweat-formation has been fully dealt with from the dermato-histological standpoint by Unna (27) in the so-called parakeratoses—*i.e.*, psoriasis, ichthyosis non-congenitalis, lichen ruber of Hebra—without any analytical details being communicated.

The first to make any quantitative estimations of the evaporation from the skin in skin diseases was Quincke (28), and under his direction O. Bieling (29). Quincke, as he states, in many eczematous conditions met with urine of a relatively high specific gravity and scanty amount in spite of the increased thirst. His method was to some extent incomplete, for only the total amount of fluid taken and the total urine passed were reckoned, the water contained in the "solid" food being neglected. The difference was regarded as water evaporation, since it was unnecessary

to take into account the evaporation through the lungs, on account of its uniform amount. The results are of the greatest value, because the numerous investigations were carried out under identical conditions. It appears from them that in a healthy person an average of 25·2 per cent., and in an eczematous subject an average of about 48 per cent. of the total intake of fluid was lost by evaporation. In addition, moist eczema appears to surpass the dry form in its amount of evaporation.

With the same methods Wilms (1) subsequently showed that in burns of the second degree the loss of fluid by the skin must be reckoned as very considerable, although in this case the secretion of fluid by the urine is very small in proportion to the intake. Reiss (30), working, it is true, with a method that is by no means free from objections, arrived at totally different results. Upon the skin to be examined he placed a bell-jar, in which the tension of aqueous vapour can be determined manometrically. This gives rise to an artificial condition, for the skin evaporation must take place in the jar just as in a more or less moisture-laden room. According to Reiss, the amount of perspiration is decreased in the skin of acute eczema, as the result of the slowing of the blood-stream, in the author's opinion. The diminution of perspiration is greatest at the centre of the diseased area ; it gradually approaches to the normal as the periphery is reached, until in the skin immediately surrounding the eruption it is actually raised above normal. Reiss states that the decrease of perspiration over skin affected by chronic eczema, lichen ruber, and psoriasis patches is still more marked, while over ichthyotic skin it is reduced to nil. Barral's results in dry eczema are identical. Similarly Leichtenstern (31), by an indirect method, calculated in myxœdema a diminution of insensible perspiration to 40 or 60 per cent., though in this case the general decrease of metabolism has to be taken into account.

Reiss found the perspiration increased in angeio-neurotic œdema (acute circumscribed œdema of Quincke), which agrees with the results of Peiper (31) and Janssen (32) on the amount of evaporation from œdematous skin. The research based upon the best method only deals, unfortunately, with a single case of ichthyosis, for which we are indebted to Schwenkenbecher (33). The patient was enclosed up to his head in a hermetically-sealed cabinet, uniformly heated and ventilated. The amount of water in the ventilating air was estimated hygrometrically. The patient was a nine-year-old boy, weighing 29 kilogrammes, with 11,600 square centimetres of skin, the subject of severe congenital ichthyosis. The loss of water from his skin amounted to 0·5 gramme per hour and kilogramme (the temperature of the cabinet was 25° to 26° C., and its relative humidity 62 to 65), a rate which, according to control experiments on healthy subjects, is at least not below, but rather above, the normal. These figures are opposed to Reiss's results. In a disease which involves so large an area as ichthyosis, the assumption of an overcompensation from the increased evaporation on the residue of healthy skin, although Reiss makes it appear quite possible, is most improbable.

3. Effect of Checked Perspiration on Temperature Regulation.

As already mentioned, the subject of Senator's experiments was kept in good health, in spite of the pores of his skin being sealed, by the fact that he was confined to bed. But under certain conditions the temperature regulation may be seriously disturbed, as was first pointed out by Tendlau (6) in an extremely interesting case.

The patient was a man with congenital atrophy of the skin in which complete absence of sweat glands was demonstrated histologically. His inability to sweat in the summer, and his consequent sufferings, drove the patient to the most extraordinary devices, for instance, when it was hot he put on a shirt that was wringing wet, and as this dried he moistened it again and again under the pump ; in summer, too, he ate only cold victuals, etc. The patient's temperature, taken whilst resting in the sun in June, rose in ten to fifteen minutes about 1° C., and reached to fever-heat. After walking about in the sun for an hour, the temperature rose from normal to 40·8° C., with all the subjective symptoms of fever, the pulse-rate being 90 to 110, and the respirations being 82. The respiratory metabolism showed the characteristics of increased lung ventilation, but in other respects was normal. In gradually cooled baths the temperature, on the other hand, scarcely fell at all. As opposed to the fact that in varnished rabbits a fall in the body heat occurs so easily, one must bear in mind the relatively much smaller surface of the human body, in the first place, and the more complete compensation of the external heat loss in man.

Linser and Schmidt (34) have described a disturbance in cases of ichthyosis similar to this, though in a much less degree. The temperature in these cases would rise much sooner and higher when placed in a room heated to 40° C., or in a hot-air apparatus, than in a normal control subject. The question raised by Schwenkenbecher, who in a case of congenital ichthyosis found the amount of perspiration normal or slightly supernormal, still requires an explanation.

III.—METABOLISM OF ALBUMIN.

1. Nitrogenous Equilibrium in General.

(*a*) *In Skin Diseases.*

From clinical facts it may be inferred that in many skin diseases a protoplasmic poison is formed which sets up a toxic destruction of albumin. Perhaps in skin diseases such as pemphigus and pityriasis rubra this is very largely responsible for the general ill-health. Reliable results as to the nitrogen balance in skin diseases are very few in number.

Stüve (35) found in one case of pemphigus vegetans upon a fixed diet of 20 grammes nitrogen per diem and 45 calories per kilogramme of body-weight a nitrogen retention of only 1 gramme per diem, which is a very

much less addition than a normal individual would exhibit under similar conditions. An unknown factor enters into Stüve's calculations in the serum exuding from the raw surface of the skin.

Selenew (241), in a fatal case of pemphigus foliaceus, found that there was no deficiency in the assimilation of nitrogen, and that it was probably increased, but suggested that the greater intake of nitrogen was balanced by the waste in the serum of the bullæ and scales.

In lichen ruber planus Radaeli (36) found an increased destruction of albumin, but only in an insignificant amount, in one case ; in three others there was no change in the albumin exchange. Spiegler, without having accurately estimated the balance, suggests that in severe cases of burns there is an increased breaking down of protein (104).

Lastly, Desgrez and Ayrignac tried to estimate the nitrogen exchange upon a basis of living protoplasm, a vague and valueless method.

(*b*) *In Syphilis.*

Considerably more work has been done on the metabolism in syphilis than in skin diseases, and there is a general agreement that in the eruptive secondary stage the albumin exchange is increased even when there is no fever, while under mercury the normal proportion returns (37). This seems to be due to a neutralization or weakening of the virus by the mercury. The total excretion of sulphates and phosphates runs parallel with the nitrogen excreted.

2. Nitrogenous Output by the Skin, and its Effect on the Balance.

There is only one point here to be considered. By the ordinary methods, the balance of nitrogenous substance is estimated by observing the nitrogen taken in as nourishment and the nitrogen output in the urine and fæces. The desquamation of the normal skin amounts only to 1 to 2 decigrammes nitrogen daily ; in the sweat only very rarely is more than 2 to 3 decigrammes nitrogen lost daily. All that remains to be determined is the loss through skin affected by some scaly or ulcerous condition, a subject on which very little work has been done.

Quinquaud (38), the first to approach this question, found in exfoliative dermatitis, particularly psoriasis, a surprising loss of nitrogen—even as much as 4·24 grammes per diem. Burgsdorf (39) estimated it in pityriasis rubra at 0·817 gramme. In a case of psoriasis closely allied to Unna's seborrhœic eczema we weighed the scales shed in nineteen hours, and found 18·823 grammes—*i.e.*, 23·78 grammes in twenty-four hours—namely, 3·12 grammes of nitrogen. Clinically the case was one of unusual severity. No estimations have been made of the albumin contained in the serous exudate from wounds of the skin. We investigated a very severe case of pemphigus vegetans which lay constantly in a bath, and by estimating the amounts of nitrogen contained in the bath-water, 5 grammes nitrogen were found to be secreted within twelve hours. The experi-

mental errors which may creep into such an analysis will, however, amount to so much in dealing with over 1,000 litres of water that this result (the only one so far worked out) must be accepted with all reserve.

IV.—SKIN DISEASES AND THE DIGESTIVE SYSTEM.

A.—INFLUENCE OF SKIN DISEASES ON THE DIGESTIVE SYSTEM.

1. General Depressant Action.

Certain general effects not characteristic of the particular skin disease are quite familiar as instances of digestive disturbances of a depressant nature—*e.g.*, scanty saliva, deficiency of HCl in the stomach, loss of appetite, retarded emptying of the stomach, sluggish peristalsis, constipation, etc. The assimilation of food, and the nitrogen and fat in the fæces, has been found normal [Radaeli (36)].

2. Saliva.

The diminution in the sulpho-cyanide reaction which may occur in the saliva in cases of syphilis is interesting. In many cases this reaction is either absent or deficient [Grober, Meuse, Joseph (40)]. Joseph considers that the syphilis is entirely responsible for this defect, and while Meuse and Mayer (41) suggest that the increased mercurial salivation is a point not to be overlooked, Joseph's tables do not admit its importance. Still, perhaps, the formation of an insoluble sulpho-cyanide of mercury interferes with the reaction. We have, however, seen cases not being treated with mercury (unless it had been administered some time previously) in which the sulpho-cyanide reaction was feeble or absent. This leads us to agree with Mayer's view that increased salivation does not entirely account for the absence of the reaction in syphilis.

B.—INFLUENCE OF DIGESTIVE DISORDERS ON THE SKIN.

There is a plethora of uncritical and unscientific views on this subject, but only one fact is clearly established, that the colour of the skin in jaundice due to biliary obstruction is the result of the depositing of bilirubin in the tissues ; this bilirubin is also the cause of the irritation.

Two classes of enterogenous dermatoses can be broadly distinguished : dermatoses *ex intestino læso*, and dermatoses *ex ingestis*. The two groups cannot be absolutely separated, for not only has the nature of the ingesta to be considered, but also the abnormal processes which may raise from a diseased organ.

1. Dermatoses ex Intestino Læso.

(*a*) *Digestive Disorders in General.*

Bouchard (42), who studied the relations of intestinal disorders to skin diseases in their broadest sense, considers dilatation of the stomach to be the chief cause of the chronic auto-intoxication to which Barthélemy (43) attributes acne ; for him every case of acne is a " stomach " case. But he diagnoses dilatation of the stomach mainly on the " succussion splash," in spite of the many objections Blaschko (44) raised to this method. According to Comby (45), Funk and Grundzach (46), dilatation of the stomach is the cause of strophulus infantum, the two latter authors including also rickets. Mitour (47) connects acne with diseases of the stomach. Blaschko and Millon, in a general way, insist upon the effect of digestive troubles in producing strophulus and prurigo, a view which the majority of German authorities support on clinical evidence [Lassar (49)]. In acute circumscribed œdema, intestinal disturbances such as abdominal pain, vomiting, and diarrhœa have been frequently described [Quincke, Weintraud (50)]. Albu (51) regards the gastritis set up rather than the food itself as the cause of urticaria *ex ingestis*.

(*b*) *Intestinal Putrefaction.*

It is generally held that some abnormal putrefactive processes occur in the alimentary canal in those skin diseases associated with gastric disturbances, but no trace of any substances of this nature have been discovered as the result of experimental dermatitis. In default of any better standard, the estimation of indoxyl and ethereal sulphates has been taken as the index of intestinal decomposition.

On purely clinical grounds, the effect of purging and " antiseptic " remedies is often quoted.

(*a*) *Aromatic Bodies.*—In urticaria, toxic, scarlatiniform erythema, acne vulgaris, and prurigo senilis, Singer (52) demonstrated a marked increase in the indoxyl and ethereal sulphates of the urine, as well as in the aromatic oxy-acids and phenol. No analysis was made of the diet or the fæces of his patients, so that his work is not of any great value.

Freund (53) describes in the same diseases " a great excess of indol and skatol, or indoxyl and skatoxyl," as well as phenol and ethereal sulphates, also marked increase of the diamines in the urine. He does not, however, give any figures, nor detail the methods he employed.

Heveroch (54) was unable to confirm Singer's and Freund's results, but his work is inconclusive. It only refers to eczema, impetigo, and dermatitis herpetiformis ; urticaria and acne are not included. Apart from this, he does not mention the total excretion of ethereal sulphates, but deals mainly with the relation between the free and combined sulphates. He also made almost all his calculations per 1,000 c.c. of urine without reference to the total amount passed. Janowsky (55) did not find any

increase of ethereal sulphates or indoxyl in the urine of two cases of prurigo. In one case of lichen ruber of Radaeli's (36), the amount of the ethereal sulphates was 0·6 gramme, and the indoxyl was decreased, although in several other cases both were normal. Gaucher and Desmoulières (56) observed that the ethereal sulphates increased in psoriasis and eczema, although it is obvious from their figures that no hard-and-fast rule can be laid down. Gans (242) has reported a case in which indican was excreted in the sweat. Engman (243), in a case of dermatitis herpetiformis, demonstrated the association of indicanuria. We ourselves have investigated two cases of acne and one of furunculosis; in only one of the cases of acne could a slight increase of the combined sulphates be shown ; the other two cases were absolutely normal.

Only one single fact can be deduced from all these results : that the amount of fermentation products appearing in the urine is markedly affected by the nature and quantity of the protein or the carbohydrates eaten. If comparable figures are desired, some definite standard for the fæces must be taken as a basis for calculations ; the frequency and consistency of the motions must be recorded. From the number of contradictory records available, it seems that in the numerous typical cases of intestinal disease in which the aromatic decomposition products were much increased skin eruptions were practically always absent. The hope of finding in the ethereal sulphates a reliable proof of the intestinal origin of any dermatosis may therefore be almost abandoned. Moreover, in those skin diseases which are associated with digestive disorders there is no evidence of increased intestinal decomposition, if the ethereal sulphates are taken as the indicator. It may be that not only are our estimations inaccurate, but that in the diseases in question a diminished resistance to the products of decomposition in the blood is produced, an idiosyncrasy which is comparable with the drug eruptions and urticaria.

(β) *Antiseptic and Antifermentation Treatment.*—Upon the disputed fact of increase of ethereal sulphates in the urine is based the chief argument in favour of an intestinal factor and a consequent antiseptic treatment of the bowels in furunculosis, acne, prurigo, strophulus, etc. Almost all authorities are agreed upon the good results following the prescription of aperient waters, etc. [Lassar (49)]. Singer advocates the use of menthol; Freund recommends large doses of ethereal oil of peppermint, with a view to the disinfection of the bowel. The treatment of furunculosis and acne with large quantities of brewer's yeast, based as it was on theoretical grounds, is very interesting, and has been acknowledged as very successful in a particular class of case [Lassar (58), Brocq (59), Hedrich (59), Roos and Hinzberg (60)].

Roos and Hinzberg believe they have isolated in a fat called " cerolin " a substance with the same properties as yeast, and have recommended it for furunculosis and acne. After repeated trials, however, we are not persuaded that there is much virtue in yeast. As to its exact effect, it is supposed to check intestinal decomposition. Quincke (60) has published his researches upon indoxyl under the yeast cure. The following table gives some results we have obtained in three cases :

Theresa A., aged 23; weight, 54 kilogrammes.

Date.	*Urine.*	*Specific Gravity.*	*Ethereal Sulphates.*	*Remarks.*
	c.c.		Gm.	
29	660	1028	0·1056	Motions formed.
30	660	1021	0·0829	Loss of urine once daily.
1	600	1024	0·0816	
2	1,120	1030	0·1308	
3	1,570	1015	0·2221	
4	570	1026	0·0916	Diet mixed throughout experiment.
5	1,040	1025	0·1800	
6	580	1015	0·1171	Yeast, one tablespoonful four times a day.
7	350	1030	0·1524	
8	560	—	0·2415	
9	360	1035	0·1701	
10	325	1027	0·1896	

Adolf H., aged 21; weight, 60 kilogrammes.—Acne Vulgaris.

Date.	*Urine.*	*Specific Gravity.*	*Ethereal Sulphates.*	*Remarks.*
	c.c.		Gm.	
1	2,180	1016	0·1796	
2	2,700	1015	0·3225	Motion once daily.
3	2,925	1012	0·3098	
4	2,060	1021	0·1895	
5	2,500	1020	0·2781	
6	3,700	1011	0·3049	Yeast, one tablespoonful three times a day.
7	3,750	1012	0·3141	
8	—	—	—	Diet mixed throughout experiment.
9	3,825	1008	0·3047	
10	3,750	1010	0·3939	
11	3,250	—	0·2187	Yeast, one tablespoonful five times a day.
12	4,075	—	0·3073	
13	3,100	—	0·3661	
14	3,275	—	0·3251	

Helene B., aged 21; weight, 54 kilogrammes.—Furunculosis.

Date.	*Urine.*	*Specific Gravity.*	*Ethereal Sulphates.*	*Remarks.*
	c.c.		Gm.	
8	1,010	1025	0·1304	
9	660	1021	0·1088	
10	920	1025	0·1529	Motions firm, once daily.
11	900	1022	0·1681	
12	650	1025	0·1473	
13	710	1026	—	
14	—	—	—	
15	—	—	—	Yeast, one tablespoonful three times a day.
16	—	—	—	Diet mixed throughout experiment.
17	—	—	—	
18	660	1026	0·1414	
19	645	1025	0·1240	
20	820	1026	0·1881	
21	850	1025	0·1739	Yeast, one tablespoonful five times a day.
22	800	—	0·1945	
23	—	—	0·2149	

In these three cases the excretion of ethereal sulphates remained evidently unaffected by the yeast, a result corroborated by von Koziczkowsky (61).

(c) *Diseases of the Liver.*

Jaundice and the irritation accompanying it are dealt with later in the section on Diseases of the Liver. In indurative cirrhosis of the liver the skin often assumes a strange thinness, dryness, and ashen tint.

2. Dermatoses ex Ingestis.

(a) *Acute Alimentary Eruptions.*

(α) *Dietetic Causes and Nature of the Rashes.*—Among the food-stuffs familiarly known to produce eruptions are strawberries and other fruit, crabs, oysters, mussels, etc., together with some which only occasionally show this effect, certain spices, asparagus, cabbages, fish, cheese, and even fresh eggs [Jadassohn (57), Bendix (62)]. The nature of the eruption is, as a rule, erythematous and urticarial, but vesicles and bullæ may occur ; speaking generally, there is a great resemblance to drug rashes.

Lewin (63) relates the case of a young man who always developed purpura after eating asparagus. What the active principle may be that causes purpura after eating crabs, strawberries, etc., is so far only a matter of conjecture ; there is no experimental basis for it to rest upon. We know that certain foods, even when perfectly fresh, may produce rashes, and, further, that fruit urticaria will sometimes disappear under an alkaline treatment. In some of the albuminous foods—crabs, fish, etc.—a toxine may be present as the result of bacterial action ; the erythema set up in botulismus (*van Ermengem's Fleischvergiftung*) is known to be due to the *Bacillus botulinus*, whose toxine may either have been formed outside the human body and survived cooking, or may be produced by the bacillus itself in the human intestine.

(β) *Theoretical Considerations.*—The view generally held is that in people with a particular idiosyncrasy some poison circulating in the blood stimulates the vasomotor nerves of the skin, or sets up an actual inflammation. From the analogy of the serum-exanthems, it is thought that in many cases the exciting cause may be of the nature of an " antitoxin." Further investigation of the specific biological albumin reactions in the blood of people with this idiosyncrasy is wanted. The question why the eruption is not universal is very difficult to answer ; does it depend on the distribution of the poison in the blood, or is the skin endowed with different powers of resistance in various parts ? Another puzzling point is the extraordinarily short time which may elapse between eating the food and the appearance of the rash " directly the taste-buds have been

touched " [P. G. Unna]; only the minutest quantity may have been taken.

Considering, too, that fright has been said to cause urticaria, Unna's theory appears reasonable that it depends upon some nerve connection between the skin and the sensory apparatus of the alimentary canal, and should be regarded, with several other dermatoses—*e.g.*, herpes gestationis—as an angeio-neurotic phenomenon, an explanation which serves also for those curious cases in which an urticaria *ex ingestis* persists for weeks or even months, although by the use of purgatives any toxine must long ago have been cleared out of the intestine [Lassar (49)].

(γ) *Experimental Evidence.*—The question of an absorptive or reflex origin for alimentary dermatoses bears closely upon another subject, whether the rashes of urticaria and erythema are angeio-neurotic or inflammatory.

Philippson (65), and Török and Hari (66), have identified a group of substances which, when injected in minute quantities, produce localized wheals. Philippson even set up urticaria in a dog by peripheral intravascular injections of peptone, morphia, and atropine. Török and Vas (67) have proved that the serous exudate of urticaria vesiculosa is richer in albumin (about 6 per cent. albumin) than the serum in anasarca, and so may be classed as an inflammatory exudate rather than as a transudate. All these experiments go to show that urticaria is inflammatory in its origin, and results from the action of some toxine upon the bloodvessels of the skin. Frisko's researches are worth mention, although his experiment scarcely produced a true urticaria. He introduced into the bowel and the subcutaneous tissues both a soluble bacterial toxine and a germ-free filtered solution of putrid maize and meat, which set up erythema, vesication, and shedding of the hair (68).

(*b*) *Chronic Alimentary Dermatoses.*

The best known are the erythematous patches of pellagra which appear on the parts exposed to the sun, the skin necrosis of ergotism, and the cutaneous hæmorrhages in scurvy. Pellagra is attributed with absolute certainty to the eating of rotten maize, from which several observers have isolated the poisonous principles. The effects of these poisons on animals can be prevented if they are mixed with the serum of a patient cured of or convalescent from pellagra [von Babes and E. Manicatide (70), Lombroso (69)]. Walker Hall fed guinea-pigs on damaged maize for several months, but was unable to produce any distinct pathological changes in the spinal cord, or peripheral nerves or organs. The chronic ergotism caused by eating " Mutterkorn " bread gives rise to vesication and necrosis of the skin of the extremities, which, however, probably depends immediately upon some disease of the central nervous system. We are quite ignorant of the cause of scurvy; probably the defective nutrition impoverishes the blood, and so predisposes to the malady.

There are also milder affections—chronic hyperæmia associated with telangiectasis and seborrhœa, developing sometimes into acne rosacea and rhinophyma—which upon the clinical evidence seem due to the abuse

of alcohol, tea, or coffee [Brocq (71), Lassar (49)]. These may well depend upon a more direct connection than Jarisch suggests in his " intestinal catarrh " theory.

Veiel (73) thinks that cheese produces acne by increasing the excretion of fatty acids through the skin. Neisser (74) denies that cheese has any effect upon a pre-existing acne, and in this we agree. Linser has recently analyzed and identified the fats in the sebaceous glands in acne.

Furunculosis, owing to its frequency in diabetes, Lassar attributes to hyperglycæmia, even without glycosuria, and he suggests that it may be caused by eating too much carbohydrate and sweetstuff; further, too, he has seen improvement follow the restriction or withdrawal of carbohydrate. Lassar's theory requires corroboration by experimental evidence as to alimentary glycosuria and the amount of sugar in the blood; for furunculosis may precede diabetes by many years. Liefmann (76), in two cases in von Noorden's clinic (examined while fasting in the morning), found the normal amount of 0·071 and 0·09 gramme sugar in the blood. It must be mentioned, however, that many authorities recommend a vegetable and carbohydrate diet in furunculosis [Güinzbourg (75)].

V.—SKIN DISEASES AND THE URINE.

A.—THE ORGANIC CONSTITUENTS OF URINE.

There is no lack of literature on the state of the urine in skin diseases, but for the most part the work is of no value, because neither the diet nor the methods of investigation are fully described.

1. Total Nitrogen.

Cf. protein disintegration (skin).

2. Water.

Cf. effect of dermatoses on the perspiration.

3. Acidity.

According to Borri, who treated the urine with calcium saccharate and then titrated with H_2SO_4 (Joulie's method), the acidity of the urine is diminished in chronic eczema, prurigo, and psoriasis (77). These diseases, according to Borri, are improved by the administration of phosphoric acid to increase the acidity of the urine. Borri's statements are, however, unconfirmed.

4. Urea.

From the work of Leredde and Radaeli (36) it appears that the percentage of urea nitrogen very often remains normal in skin diseases,

though in many cases it is increased or diminished. In one case of lichen ruber planus Radaeli found it as high as 90 to 93 per cent., the quotient $\frac{\text{Urea nitrogen}}{\text{Total nitrogen}}$ falling, however, under arsenical treatment during a relapse to 70, or even 66. Under similar conditions in psoriasis the same result was observed—a fact that is chiefly of pharmacological and toxicological interest. Fever may play some part in lowering this quotient. This probably occurred in a case of dermatitis herpetiformis, where Wickham (78) found it 78·2 and 78. But similar results were arrived at by Gaucher and Desmoulières (56), and Desgrez and Ayrignac (79), in psoriasis and eczema, where fever was absent and the amount of ammonia was normal.

In two cases of tertiary syphilis von Jaksch [80] noted a decrease in the urea nitrogen and an increase in the amido-acid nitrogen. This lacks confirmation, and von Jaksch himself has admitted that the method employed was not wholly free from objection.

5. Ammonia.

Radaeli (36) found the amount slightly decreased in lichen ruber planus. Linser and Schmidt (34) observed that it was normal in acne and ichthyosis. Gaucher and Desmoulières (56) found similar results in eczema and psoriasis.

6. Uric Acid.

The uric acid excretion was normal in amount in lichen ruber [Radaeli (36)], in eczema and psoriasis [Gaucher (245) and Desmoulières (56)], in alopecia, mycosis fungoides, erythema scarlatiniforme, psoriasis, and eczema [Desgrez and Ayrignac (79)]. Although the two latter authors describe an increased excretion of uric acid as the result of nuclear destruction in many dermatoses, they base their opinion less upon the actual amount of uric acid that they found than upon the quotient $\frac{\text{Uric Acid}}{\text{Urea}}$, which was increased in many cases, a very untrustworthy conclusion. In acne the alloxur bases were normal [Linser and Schmidt (34)], or, at any rate, not decreased [Gaucher and Desmoulières].

7. Albuminuria.

Cf. kidney diseases and the skin.

8. Albumoses.

According to Wilms, albumoses are a regular constituent of the urine after severe burns, making their appearance immediately after the injury.

9. Hæmoglobin and Hæmatoporphyrin.

Hæmoglobinuria has been frequently observed in cases of acute circumscribed œdema [Joseph, Roques, Wendt (81)]. Exposure to cold may be responsible for both the skin affection and the hæmoglobinuria. Syphilis comes into the past history of one large class of cases of paroxysmal hæmoglobinuria, the actual onset being often excited by a "chill." In the hæmoglobinuria of acute circumscribed œdema it must be assumed that the red corpuscles are so peculiarly sensitive to cold that they break up very easily. Lesser's (84) idea that hæmoglobinuria always follows extensive burns is not confirmed by Dohrn (85), and Lichtheim (86) regards it as only an occasional symptom. Hoppe-Seyler (82) describes a methæmoglobinuria after burns, in which the blood-corpuscles [as Max Schultze (83) demonstrated microscopically] break up under the direct action of the heat. As an instance of hæmatoporphyrinuria with skin diseases, MacCall Anderson's (87) examples of two brothers with hydroa æstivale may be quoted [see also Linser (246)].

10. Sugar.

Alimentary glycosuria occurs frequently in psoriasis [Nagelschmidt (88)]. (See also Diabetes and Skin Diseases.) Increase of the fatty acids has been described in acute exanthemata. Frerichs found valerianic acid in small-pox, but this may be more properly attributed to the febrile process itself.

11. Pigments.

Garrod (247) has drawn attention to the combination of alkaptonuria with the peculiar pigmentation of cartilages and skin known as ochronosis ; in eleven cases of ochronosis collected by Garrod, four cases presented alterations of pigment in the skin. The rarity with which alkaptonuria occurs, and the appearance in the urine of somewhat similar pigments which do not contain homogentisic or uroleucic acid, makes the explanation of the problem of abnormal pigmentation the more obscure. Garrod, at least, believes that alkaptonuria is one, but not the only, cause of ochronosis.

Surveyor (89) has described a pigment which was present in the urine in febrile vesicular eruption on the face. A rose-violet colour was produced by the addition of NaOH to the urine ; reducing agents caused a paler, oxidizing agents a deeper colour. The pigment itself was insoluble in water, alcohol, and ether.

12. Toxines.

(*a*) *In Skin Diseases and Syphilis.*—Chatinière (89) reports that the urine of a leper in the tubercular stage of the disease was less toxic than in healthy subjects. Calderone (90) agrees as to the urine, but claims that

the toxicity of the serum in a similar case was slightly increased ; while Fisichella (91) found the toxicity of the urine increased.

The urine has been described as more toxic than usual in Werlhof's disease [Carrière and Gilbert (92)], in pemphigus vegetans [Pini (93)], in psoriasis [Oro and Mosca (94)], and in eczema papulo-squamosum and general ichthyosis [Colombini (95)].

Griffith isolated in eczema a ptomaine, " eczemin," which, when injected into rabbits, caused fever and death (96). Tête and Vandame (97) have done the like in dermatitis herpetiformis. The toxicity of the urine in Tendlau's case of atrophy of the skin (5) was, at any rate, not increased, and Colombini (95) states that it was constantly reduced in moist eczema (*e.g.*, eczema rubra madidans) to more than a half ; this he attributes to the increased excretion of toxines by the skin, the diminished excretion by the urine being possibly the cause of the disease. Lastly, Soual (98), whose work is of doubtful value, reports that the toxicity of the urine is decreased in the first two years of syphilis.

The researches on this subject are not very reliable, the conclusions being frequently based upon a single case. The methods of estimating toxicity are so far quite inadequate, while observers are divided in their opinions as to whether increased toxicity in the urine means that more toxine is produced in the system, or whether diminished toxicity is due to a retention of toxine in the system.

(*b*) *Burns.*—Upon one point, at least, it is agreed : that in burns toxicity of the urine is increased, but never decreased.

Catiano (99) and Lustgarten (100) are responsible for the theory that death from burns is due to absorption of toxines produced by bacteria on the injured surface. Kijanitzin (101) found in the urine, and also in the blood, of such cases a ptomaine similar to Brieger's " peptotoxine," which proved very fatal to animals. Ajello and Parascondolo (102) have corroborated these results. Reiss (103) has identified certain " empyreumatic " substances, especially pyridin, in the urine in several cases. Spiegler (104) and Wilms (29), who on theoretical grounds do not regard pyridin as the cause of death, still found it present in nine out of twelve cases. Spiegler and Frankel (105) observed many other substances, to which they only refer in general terms. It is by no means certain whether the supposed toxine is formed by the burning of the tissues, or arises from the blood they contain, or originates from some general systemic reaction. Spiegler was unable to produce any toxic effect with an extract made from human skin which had been burnt after death ; but Weidenfeld (106), by grafting burnt skin into the peritoneal cavity of guinea-pigs, caused illness and death. This has, however, been since contradicted by Helstedt, but corroborated by Eijkman and Hoogenhuyze and Pfeiffer (248). Scholz (107) demonstrated that burning the ears of rabbits was not fatal if the ear was first rendered bloodless, arguing from this that the toxine was formed by the heating of the blood [Pfeiffer].

In fact, although the exact nature of the toxines has not yet been established, the view is rapidly gaining favour that toxæmia plays the chief part in the pathology of burns.

B.—EXCRETION OF THE MINERAL SALTS.

Owing to the exact "salts balance" not having been taken into account, many of the following results lose a good deal of their importance; some of them are remarkable enough from the conclusions based upon them.

In the urine of syphilitic patients Soual (108) observed an increase of chlorides, the proportion of chlorides to urea, which is usually 1 : 2, being raised to 1 : 0·7—a result whose importance cannot yet be properly gauged. In his investigations upon various skin diseases, especially prurigo, Grosz (109) took into consideration the chloride intake, and his results are accordingly more reliable; he came to the conclusion that the chloride output was increased, but that in skin diseases periods of chloride retention alternated with periods of increased elimination, an idea which seems quite compatible with the known relations of sodium chloride to the water in the tissues; unfortunately, Grosz only happened on the periods of increased secretion. Jacquet and Portes (110) assert that they met with increased output of inorganic bodies in proportion to organic in the urine of a patient with alopecia; the chlorides were increased while the phosphates and sulphates were diminished. The observations upon this case led them to associate the increase of chlorides in the urine with the decrease of chlorides and alkalis in the blood.

Campana and Condelli (111) found in certain neuropathic "dermatoses" an increase of alkaline salts in the urine. This agrees with Soetbeer's researches on phosphaturia (112).

VI.—SKIN DISEASES AND THE BLOOD.

A.—EFFECT OF DERMATOSES ON THE BLOOD.

It is not easy to distinguish clearly between blood changes which are the direct effect of skin disease and those which may be regarded as due to a general disturbance of nutrition. As a rule, such changes as have been observed take the form of a decrease in the blood density, a deficiency of red corpuscles and hæmoglobin, or relative and often absolute increase of leucocytes. These changes are so common that they must be reckoned rather as a sign of ill-health in general than as a characteristic of any particular disease. It is also quite clear from the literature on the subject that the blood changes depend more upon attendant circumstances than upon the skin lesions primarily. For instance, anæmia has been ascribed to almost every skin disease, but the same diseases are often reported unaccompanied by anæmia; and we know that without any blood change sleeplessness and loss of appetite from skin diseases will produce a pallor of the skin and mucous membranes which may be explained by some defective filling of the bloodvessels generally and a reduction of the amount of blood, a matter of which little is yet known.

1. Blood Concentration.

(*a*) *Skin Diseases.*

On *a priori* grounds the concentration of the blood may be expected to be altered in many skin diseases. The increase of perspiration, the extension of the disease to secreting surfaces, or the draining of fluid from the blood into the pustules, would suggest that some change in the density of the blood and serum may result—an increased viscosity if we argue from other pathological experiences—although in chronic nephritis with a constant drain of albumin from the blood hydræmia may coexist [Quincke (28), Bieling (29), Rzetkowski (249)]. Schlesinger's researches (113) by Hammerschlag's method point rather in the former direction. In pemphigus the specific gravity of the blood remained practically normal, or very slightly raised. During the eruption of the bullæ there was often a marked, but short-lasting, increase in the blood density, while the serum density was hardly affected, so that evidently a decrease of the total serum bulk results from the flow into the bullæ. In moist eczema the blood density is normal, with occasional viscidity, and even after long continuance of the disease and consequent anæmia the blood density is very little altered, while but rarely is there a deficiency of albumin in the serum.

A marked increase of the blood density has been reported as the result of severe burns [Baradue (114), Tappeiner (115), Schlesinger and Hock (116)]. According to the latter it fluctuates between 1065 and 1073, and in the course of two days after the accident often falls again.

The phenomena have not yet been explained. Tappeiner's theory of the transudation of a fluid rich in plasma into the tissues does not hold good for all cases. The specific gravity of the serum in the bullæ of vesicular eruptions is, as a rule, slightly below that of the blood-serum, although in herpes zoster it is exceptionally high. Schlesinger gives the following table :

Skin Affection.	*Specific Gravity of Serum in Bullæ.*	*Specific Gravity of Blood-serum.*	*Average Density of Serum in Bullæ.*
Urticaria	1028–1030	1031 –1031·5	1028·5
Erythema multiforme ..	1025–1029	1030 –1031·5	1026
Erysipelas bullosum ..	1025–1030	1030 –1031	1027
Pressure blisters ..	1023–1024	1029 –1031	1023·5
Eczema	1021–1028	1029·5–1031	1022·5
Artificial blisters ..	1019–1027	1029·5–1032	1024·5
Burn blisters	1019–1029	1028·5–1031·5	1025
Vaccine vesicles ..	1027–1029	1030·5–1031	1028
Pemphigus	1018–1030	1028 –1032	Very variable.
Herpes zoster	1031–1042	1029 –1031·5	1036

The blood density was found to be normal in a lichen ruber without cachexia, leprosy, psoriasis, idiopathic multiple pigmentary sarcoma, prurigo, and erythema multiforme, while in the acute hæmorrhagic skin diseases—*e.g.*, morbus maculosus Werlhofii—it falls considerably.

(*b*) *Syphilis.*

In syphilis the blood density is very variable. From the analogy of the other blood changes in this disease it may be fairly correct to infer that a decreased density is the rule ; but the reports are very contradictory [Valerio (117), Verrotti (118), Dacco (119)].

2. Erythrocytes and Hæmoglobin.

(*a*) *In Skin Diseases.*

When the general health is unaffected, the blood count shows no change in either red corpuscles or hæmoglobin, although probably many skin diseases affect by preference anæmic persons [Dacco]. Changes corresponding to anæmia gravis are described in pemphigus [Radaeli (36)], leprosy [Winiarski (120)], xerodermia pigmentosum [Okamura (121)], sarcomatosis cutis [Kaposi (122)], pityriasis rubra [Jourdanet (123)], severe syphilis, and other dermatoses ; although in almost all of these diseases the blood count has in some cases been absolutely normal, when perhaps the decrease of the total blood bulk referred to previously may account for the pallor of the patients.

In eczema, psoriasis, dermatitis exfoliativa, lichen ruber planus, prurigo, acne, and lupus vulgaris, Dacco found the red corpuscles and hæmoglobin normal, although in some cases there was slight anæmia. Radaeli (36) found no alteration in seven cases of lichen ruber. In erythema there is often a slight anæmia [Neumann (124)]. In psoriasis, according to many observers [Zelenew (125) and others, but not Schlesinger (113)], a deficiency of hæmoglobin occurs, as in chlorosis. In gonorrhœa a fall in the red corpuscles and hæmoglobin has been demonstrated [Giorgi (126)], though Eserteau (127) found the blood count normal as a rule, with occasionally a slight anæmia.

(*b*) *Burns.*

In extensive burns one naturally meets with the most destructive changes. The blood-corpuscles shrivel, become crenated, or break up into the form of microcytes and débris, or lose their hæmoglobin and become mere outlines (83, 128).

The blood-corpuscles probably succumb to the direct effect of the heat. Their remains may block the smaller vessels and produce thromboses. By such means it is supposed that ulceration of the stomach and duodenum is caused, although Wilms (1) and Weidenfeld (106) have thrown considerable doubt on these occurrences, and have actually demonstrated a diminished coagulability of the blood in burns.

Lesser regards the destruction of blood-corpuscles as the direct cause of death. Hoppe-Seyler (82) has raised the objection, however, that even in severe and extensive burns the number of corpuscles destroyed

and the amount of hæmoglobin liberated are relatively very small. If the whole surface of the body were burnt, about 5 per cent. of the corpuscles might be destroyed—*i.e.*, if the total mass of blood were 5 kilogrammes, some 5 grammes of blood would undergo disintegration.

The red blood-corpuscles sometimes rise to 8,000,000 per c.c. in severe burns, a number which stands in relation to the increased viscosity [Tappeiner, Wilms].

(*c*) *Syphilis.*

Diversity of results and theories characterize the work on so protean a disease as syphilis. Its various stages, its universal distribution in great cities, and its coincidence with other diseases, all tend to make the research difficult and inconclusive.

In older works the destruction of red corpuscles was emphasized (129). The decrease in hæmoglobin has also been pointed out (130). Radaeli (130) compared the anæmia of the secondary stage to that of chlorosis. Becker (146), Smirjagin (131), and Verrotti (118) attach no importance to a deficiency of red cells in secondary syphilis. Other workers allow that it occurs constantly in a slight degree (130, 136, 132, 119). Opinions differ as to the time when the blood changes start. Some place them in the primary stage only (130, 133) ; others exclude the primary stage [Rille (134)].

Neumann and Konried (135, 136) described an oligocythæmia and oligochromæmia as peculiar to the tertiary stages. The red corpuscles seem to be more frequently affected in hereditary syphilis in children than in adults with the acquired form. Loos (130), in mild cases of hereditary syphilis, found the number of red cells practically normal and the hæmoglobin slightly deficient, while in more severe cases there was fairly frequently marked poikilocytosis with megalocytes and microcytes, polychromatophilia, and a great increase of nucleated red cells, together with siderosis of the liver and spleen.

Blood platelets have been described in a case of syphilitic anæmia [Losdorfer and Vörner (137)]. Several authors who have studied the question of the resisting power of the erythrocytes in syphilis have reported that it is more or less diminished (117, 118, 138).

It is unanimously agreed that under mercurial treatment the blood is soon restored to its normal state [Bieganski (130), Oppenheim and Löwenbach (132), Reiss (130)]. Justus (139), whose observations extended over a long time, describes a sudden fall in hæmoglobin just at the beginning of the administration of mercury. This he attributes to the diminished resistance of the red cells, and regards it as a diagnostic sign and specific reaction of syphilis.

The investigations of Cabot, Martins, and D. H. Jones are actually reliable, but those of the majority of authors (132, 136, 140) yield such contradictory results that Justus's reaction may no longer be considered as absolutely diagnostic. In one class of case, however, the deficiency in hæmoglobin was observed before the mercurial treatment was begun [Feuerstein (136), Oppenheim and Löwenbach (132)].

Samberger (138) describes an increase of urobilin in the urine at the beginning of the mercurial treatment, which he attributes to a "pleiochromia," from the destruction of blood-corpuscles, with a subsequent increased formation of urobilin in the intestine.

3. Leucocytes.

Leucocytosis is very common, though not absolutely constant, in many skin diseases, except, of course, in those which arise from leuchæmia; but the variations in the differential count are of more interest than the absolute increase of leucocytes.

(*a*) *Leucocytosis, with Relative Increase of Polynuclear Cells.*

The leucocytosis seen in many cases of lichen ruber, eczema, syphilis, and mycosis fungoides belongs to this class [Radaeli (36), Dacco (119), Oppenheim, Löwenbach, and Loos]. In those cases of pemphigus in which pronounced eosinophilia is absent, the polynuclear neutrophile cells are often increased at the expense of the lymphocytes, the large mononuclears and the transition forms remaining unaffected [Radaeli]. In erysipelas an almost complete polynuclear leucocytosis, with absence of the other cells, especially eosinophiles, is described [Zappert (141)].

(*b*) *Leucocytosis with Relative Increase of Lymphocytes.*

According to Dacco, this occurs almost constantly in psoriasis, the polynuclear cells showing considerable decrease. In prurigo the same change is found with simultaneous increase of eosinophiles (142, 150). A characteristic lymphocytosis has recently been described in pellagra, with a slight absolute leucocytosis (143). It is remarkable that such an important change should have been previously overlooked, for Neusser (143) found only an eosinophilia.

A special interest attaches to mycosis fungoides on account of the suggestion that it may be due to a lymphadenia of the skin. In spite of the simple polynuclear leucocytosis described by Fabre, Lukasiewicz, Wolters and Sereni (145), pronounced lymphocytosis [even 60 per cent. of lymphocytes, Allgeyer] has been so often found [Bensaude, Leredde, Allgeyer, Jadassohn, Ebstein-Schwalbe (144)] that it is very difficult to deny that the blood changes may have a positive pathognomonic importance in a disease such as this, where the diagnosis is so difficult. The idea is gaining ground that mycosis fungoides should be classed among the dermatoses secondary to diseases of the blood [Brandweiner, Radaeli (250)].

According to the majority of writers, secondary syphilis is usually associated with considerable leucocytosis, in which the lymphocytes preponderate. Virchow noted this in 1869, and attributed the lymphocytosis to the general adenitis. The authorities differ. Bieganski, Antse, Rille and Becker (146), report a slight leucocytosis with marked

increase of lymphocytes ; Dacco, Oppenheim and Löwenbach, and Hauck (252) were unable to note a lasting leucocytosis in the secondary stage ; Radaeli (130) maintains that there is no absolute leucocytosis, only a relative increase of polynuclear cells at the expense of the mononuclear and transition forms ; Dacco (130), Sabrazès and Matthis (132), and Verrotti (118) only met with lymphocytosis in five cases out of thirty. Radaeli and Loos (130) have recorded the presence of myeloplaques in the blood in severe cases.

Cabral de Lima (251), in an examination of twenty-five cases of leprosy, found a constant deficiency of polynuclear cells (23 per cent. to 69 per cent.), an increase of lymphocytes in all save one case, the large mononuclears being increased in sixteen cases, normal in eight, and decreased in one case, but the total of lymphocytes and large mononuclears together was in every case above the normal. There was no constancy in the number of eosinophiles ; they were found in some cases increased, in others normal or diminished. The mast cells were in every case normal.

(*c*) *Eosinophilia.*

This change has been described both in the blood and the serum of the bullæ in pemphigus [Neusser, Gollasch, Lukasiewicz (143), Canon (147), Selenew (241)], also in pellagra, eczema, prurigo, psoriasis [Canon] ; but it appears to be confined to a small group of skin diseases. It only occurs in a proportion of the cases of eczema ; in the artificial—occupation —varieties it is generally absent [Peters (142)]. In psoriasis eosinophilia rarely occurs. The same remark may be applied to syphilis [Rille and Peter].

The diseases in which eosinophilia most constantly occurs are pemphigus and prurigo. In the latter the percentage of eosinophiles may reach 17·2 per cent., and even in the mildest cases rarely falls to 2·5 per cent. [Peter, an analysis of thirty-one cases]. This sign may be of value in the differential diagnosis between prurigo and certain cases of urticaria, strophulus, etc., although it is not absolutely pathognomonic of prurigo [Jadassohn]. Owing to the doubtful etiology of prurigo, perhaps a separate class should be made of those cases associated with eosinophilia.

Leredde some years ago similarly proposed to differentiate dermatitis herpetiformis of Dühring, pemphigus foliaceus and vegetans from pemphigus vulgaris, because it was only in the former diseases and their near allies, herpes gestationis and Wilson's hydroa vacciniforme, that a simultaneous eosinophilia of the blood and serum of the bullæ is met with (153). On the other hand, many authors (amongst whom we count ourselves) entirely reject Leredde's theory [Gaucher and Claude, Hallopeau, Jadassohn, Kaposi (154), Radaeli (36), Dacco (119)]. However, the question must remain unsettled so long as, clinically, many cases of dermatitis herpetiformis cannot be distinguished from pemphigus. Eosinophilia in the bullæ is hardly ever seen apart from pemphigus. Bettmann (155) found it absent in the bullæ of eczema, herpes labialis, varicella, miliaria, and in nine cases of herpes zoster, while it was very

pronounced in the tenth. Darier (153) in a case of leprosy with 61 per cent. eosinophiles in the blood, could not demonstrate eosinophilia in the bullæ. Gaucher, Barbes and Claude (154), on the contrary, found eosinophiles in the bullæ of herpes and ecthyma, and Sabrazès in dyshidrosis. It is remarkable that in cases of burns eosinophilia is found neither in the bullæ nor in the blood [Neusser and Bettmann].

No obvious connection exists between the number of eosinophile cells in the blood and in the bullæ, for the blood may be rich in them, while they are absent from the bullæ, and *vice versa* [Gaucher and Bensaude (155), Darier (153), Bettmann].

Neusser has observed that eosinophilia only occurs in the " pathognomonic " form of pemphigus, and is absent from blisters raised artificially. Bettmann, who was unable to corroborate this, suggests that the age of the bullæ may affect the question, and that eosinophile cells are only found when the blisters are quite fresh.

A very important case of pemphigus has been published by Neusser (143), in which, notwithstanding marked eosinophilia in the blood, the marrow in the long bones was normal. Neusser and Rille (134) claim from this that eosinophile cells may be actually formed in the skin, in spite of the general view that they take their origin from certain structures in the bone-marrow [Ehrlich (156)].

The general pathological importance of eosinophilia is very great, although the exact etiological factors are not yet determined.

Diseases in which eosinophilia exists in the blood associated with skin affections are bronchial asthma and certain parasitic diseases, such as trichinosis and filariasis. The combination of asthma with dermatoses—*e.g.*, psoriasis and eczema—has often been described.

Further research is necessary in order to define the laws which govern these remarkable coincidences. If eosinophilia were carefully studied in its relation to the various stages of the disease in which it occurs, some fresh light might be thrown on the subject. It is certain, for instance, that asthma is associated with a considerable, though transient, eosinophilia in the blood. The eosinophilia only exists during certain stages of the asthmatic attack, and disappears in adults who have suffered long from it, or in whom a chronic muco-purulent bronchial catarrh is present. Such periodic variations and interdependence of complications will most probably be observed in connection with skin diseases.

A new chapter has, however, been opened by the more recent investigations upon the phagocytic powers of the eosinophile cells [Wright (253)]. A general discussion of the subject is to be found elsewhere, but brief mention should be made of the altered rate of phagocytosis manifested by the eosinophile cells in certain diseases of the skin. Bushnell and Williams (254) have demonstrated a diminution in the phagocytic power of the eosinophile cells of the blood in a case of dermatitis herpetiformis.

(*d*) *Mast Cells.*

These are slightly increased in psoriasis, eczema and prurigo [Canon (147)]. In pemphigus foliaceus the proportion of mast cells has been

found to rise from the normal 1 : 400 to 1 : 100. Basophile mononuclear cells may increase in this disease, but more especially in urticaria pigmentosa [Leredde (158)].

4. Alkalinity of the Blood—Isotonia.

Tschlenoff (159) reports that the alkalinity of the blood is normal in favus, herpes tonsurans, pruritus, alopecia, lupus, tuberculosis cutis, atrophy of the skin, but is slightly diminished in diseases which may interfere with the general health, such as sclerema, dermatitis herpetiformis, purpura, eczema, erythrodermia, pemphigus, psoriasis, erythema exudativum, lichen ruber [Landois' method (159)]. Dacco (160) confirms these results in the main, but finds that in eczema the degree of alkalinity, although frequently diminished, varies in some way with the outbreaks of the eruption. Radaeli (36) and Dacco (188) found the alkalinity normal in lichen ruber.

Seeing that actual decrease in alkalinity has only been proved in severe cases of diabetes, in very acute fevers, and in the last stages of inanition, these results in skin diseases must be accepted with reserve. Methods for the determination of the alkalinity of the blood are as various as they are unreliable. Radaeli (36) found the isotonia of the blood normal in lichen ruber.

5. Proteins of the Blood—Toxines and Antitoxines.

Jolles and Oppenheimer (161), working with the method suggested by Jolles (volumetric estimation of nitrogen gas) upon the albumin of the blood in the several stages of syphilis, found that the amount was constantly normal, and was unaffected by treatment.

Quinquaud (161) claims toxic properties for the blood-serum in generalized eczema ; and in cases of burns many authors who described toxines in the urine have found the same in the blood [Kijanitzin, Dohrn (101)]. According to Dietrichs (162), auto-, iso-, and heterolysin, also agglutinin, are formed in the blood of guinea-pigs who have been subjected to scalding, though Kreibich (163) contradicts this.

Our knowledge, however, of substances of this kind is very scanty. We can only speak in general terms of a theoretical action of " antibodies," cytotoxines, and cytolysins, in regard to the production of many dermatoses. Even if it is going too far to suggest that the exanthems of pregnancy—*e.g.*, herpes gestationis—are the expression of some reflex action of cytolysins through the central nervous system, yet the probability of some of the complications in pregnancy, such as nephritis, being due to their local effects is very great.

Food eruptions and the enterogenous dermatoses, particularly those caused by errors in metabolism—*e.g.*, diabetes mellitus, etc.—seem almost irresistibly attributable to a reaction of the organism to the presence of protein derivatives or pure proteins into the blood.

The whole group of skin affections which occur at puberty suggest that the generative organs pour into the blood some secretion which possesses cytolytic and chemiotactic properties, and whose affinity for the cells of the skin sets up there an inflammatory reaction. It is well known that the most careful attention to the skin will not prevent these dermatoses of puberty, and, clinically, the only explanation that seems possible is that the supply of the irritant is being constantly renewed by the blood.

6. Serum Exanthems.

These eruptions present a type of the skin disease which manifests itself as the reaction of the organism to some highly complex molecular compound introduced into the system. Formerly it was supposed that the rashes were merely the mechanical result of precipitation in the blood-stream obstructing the circulation [Hamburger and Moro (164)], but this theory is untenable, since Rostosky, Oppenheimer and Michaelis have proved that precipitation does not take place in living blood (165). But, apart from the absence of precipitation in living blood, no absolute connection can be established between the formation of precipitin and the serum eruption, for, on the one hand, precipitin does not appear until long after the rash, and, on the other hand, a severe rash may be quite unaccompanied by precipitin [Francioni, Marfan, Pirquet and Schick (166)].

Still, it is most probable that the serum exanthems do in some way depend upon antibodies formed by the organism in response to the serum injected. If they are not identical with precipitin itself, they are, at any rate, concerned in some unknown manner with the formation of antitoxine.

Very little is known, unfortunately, of the proteins, which, from their peculiar nature, or from defective absorption due to disease of the intestine, find their way into the blood, nor is the part played by the absorption of the antibodies thus produced sufficiently understood to enable us to fully explain the origin of the enterogenous dermatoses (*ab ingestis* and *ab intestino læso*). We can only surmise that in some such process is concealed the secret of the autotoxic dermatoses.

B.—EFFECT OF BLOOD CHANGES ON THE SKIN.

No sharp border-line separates the influence which diseases of the blood or blood-forming organs exert upon the skin. From the foregoing chapter it seems probable that the dermatoses mentioned are not examples of primary diseases of the skin directly affecting the blood, but, rather, that the skin changes, and the increased amounts of eosinophile cells which find their way from the bone-marrow into the blood and bullæ, are the simultaneous results of some poison circulating in the blood. Leredde (151) has suggested that the pathological changes in the marrow and blood may be the primary and determining factor in the dermatosis. Mycosis fungoides is an instance of a disease which has

been variously explained as being primarily either a skin disease or a lymphæmia.

With so many border-line cases in which cause and effect are indistinguishable, there are few enough skin diseases left of which we can say that, clinically, the disease of the hæmopoietic system is the primary factor. The chief instances are purpura, morbus maculosus Werlhofii, etc., and the skin changes of leuchæmia and pseudo-leuchæmia (255).

The cutaneous hæmorrhages which characterize purpura[1] and the allied conditions we are accustomed to regard as secondary, because pathological—*i.e.*, inflammatory—changes are absent. In this category come also the cutaneous hæmorrhages of certain poisons like the aniline arseniates, and of jaundice, etc. [Herringham (257)].

1. Hæmorrhagic Diatheses.

The particular toxine in the blood which is the cause of the hæmorrhagic diathesis is still unknown, so that, in discussing the blood changes in this condition, it must be remembered that the changes themselves are probably only symptomatic, and are concomitant with, rather than causal of, the skin condition [Sahli (257)]. Hayem (167), after careful investigation, suggests that the coagulability of the blood may be altered in purpura. Possibly the coagulum does not separate properly from the serum (deficient transudation of serum, deficient contraction of clot). Morphologically, the number of blood platelets may be less than normal. Bensaude and Sicard agree with Hayem (168 and 169), but Apert and Allacia (170 and 171) were unable to confirm Hayem's results. Very contradictory statements have been made not only as to the behaviour of the serum, but also as to the red and white corpuscles in purpura.

Apert and Allacia found the red cells and hæmoglobin to be subnormal. Spietschka (172), on the contrary, observed numerous nucleated red cells in two cases of purpura with profound anæmia.

Lenoble (173) distinguished the following blood changes :

1. A *purpura myéloide.*
2. Purpuric eruptions with slight *réaction myélocytaire.*
3. Simple purpuric eruptions.

He considers " deficient contraction of the clot and deficient transudation of serum " [Hayem Bensaude] characteristic of myeloid purpura, while it is accompanied by the appearance of nucleated red cells (chiefly normoblasts), of myelocytes (usually neutrophile, sometimes eosinophile), and a scarcity of hæmatoblasts, which show a tendency to disintegration and the formation of clumps.

[1] The term " purpura " covers several conditions of widely differing etiology. Unna distinguishes the following varieties :

1. Bleeding *per rhexis*, as in hæmophilia, due to deficient retraction and elasticity of the arterioles of developmental origin.
2. Bleeding *per diapedesis*—
   (*a*) From hypostatic congestion in marasmic conditions ;
   (*b*) From obstruction of capillaries by bacterial emboli or fragments of growth ;
   (*c*) From direct changes in the capillaries—*e.g.*, amyloid, toxic, etc. ;
   (*d*) From spontaneous clotting with disintegration of hæmatoblasts [Hayem].

Occasional changes met with are :

Slight leucocytosis (10,000 to 25,000 per centimetre), with relative increase of lymphocytes, hæmoglobin reduced out of proportion to the red corpuscles, and unusual reticulation (*Eigentümlichkeiten des "Reticulums"*).

Purpura with *réaction myélocytaire attenuée* is characterized by the presence of myelocytes and of transition forms between these and neutrophile polynuclear cells ; while the transudation of serum is often normal, and the hæmatoblasts, erythrocytes, and leucocytes are, as a rule, in normal amount.

The so-called simple purpuric eruptions are those in which the blood shows no particular changes, either in the number or form of its corpuscles.

A single case of purpura hæmorrhagica apparently cured by the rectal injection of antistreptococcic serum is by itself of little value in explaining the condition, but it may serve to direct attention to a toxine as the probable cause of this condition [Fenwick and Parkinson (258)].

2. Leuchæmia and Pseudo-leuchæmia.

The cutaneous hæmorrhages in leuchæmia and pseudo-leuchæmia present more varied appearances than does the hæmorrhagic diathesis ; indeed, dermatology is flooded with a wealth of detailed statements on the subject. From these the following classification may be selected :

1. Eczematous and lichen-like eruptions.
2. Diffuse infiltration and thickening of the skin, with swollen folds of skin separated by deep furrows (facies leontina) (174).
3. Circumscribed tumours, varying in size from a pin's head to a fist, with diapedesis of blood (175, 259).
4. Intense irritation, with swelling of glands not involving the skin [Dubreuilh (260)].
5. Cutaneous hæmorrhages.

Hitherto the occurrence of tumours has only been described in lymphatic leuchæmia, and very rarely in myelogenous leuchæmia, although we have seen it in the latter disease ourselves. White flat tumours appear on the lower limbs, the skin being only slightly movable over them. Similar changes in the skin of a more protean character are met with in pseudo-leuchæmia ; sometimes they are pruriginous or lichen-like rashes [Wagner, Joseph (176)], sometimes they are eruptions comparable to pityriasis rubra [Peter (178)], sometimes they are dermatoses which are barely erythematous [Wassermann (179)], sometimes they are tumours [Arming, Unna, Fröhlich (177)]. Many authorities are undecided whether the prurigo is not perhaps the primary event, and the tumour and lymphæmia associated may not result from the excoriation of the skin [Peter, Lassar]. To this class probably belongs the disease described by Kaposi (180) as "lymphodermia perniciosa." Lastly, it is possible that many cases of mycosis fungoides are the expression of primary changes in the hæmopoietic system, especially those in which

enlargement of glands and lymphocytosis are present [Paltauf, Pinkus (181, 175), Brandweiner and Radaeli (250), Ramazzotti (261)], although a reaction in the blood set up by the primary tumours cannot be excluded. Moreover, apart from leuchæmia and pseudo-leuchæmia, skin diseases, of perhaps less importance, occur in connection with minor changes in the blood and blood-forming organs.

Buschke (182) mentions a pruriginous eruption in the chronic splenic enlargement of malaria. Dacco has drawn attention to the numerous skin diseases to which anæmic and chlorotic subjects are prone. There is Hebra's example of the woman after childbirth who only developed eczema when simultaneous manifestations of profound chlorosis appeared. Indeed, clinical experience confirms again and again the fact that the best way to improve a girl's complexion is to cure her chlorosis.

3. Urticaria.

Wright (183), in his investigation of " serous hæmorrhages "—*i.e.*, transudation of serum into the connective-tissue spaces in urticaria—lays great stress upon the delayed clotting of the blood, a similar change to that described by Hayem in purpura (167). This diminished coagulability may depend on the combination of certain organic acids with the calcium salts in the blood, thus explaining the curative effects of the administration of calcium chloride. These suggestions, however, lack confirmation.

Further researches into the etiology of urticaria, with special reference to the coagulation of the blood, have been carried out by Little and Paramore (262). Conclusive results have not yet been obtained, but there is considerable evidence to show that at least in some cases of urticaria the chemical constitution of the blood is abnormal, and that the salt content of the blood is materially altered

VII.—DISEASES OF THE SKIN AND THE KIDNEYS.

A.—EFFECT OF SKIN DISEASES ON THE RENAL FUNCTIONS.

The close connection between the skin and kidneys has already been made evident. These organs excrete similar substances, and may on occasions do duty for one another, while the absorption of fluids by the intact or raw skin takes place so readily that irritation of the kidney may be set up in this way.

1. Experiments on Animals.

The connection between the skin and kidneys has been demonstrated by experiments. Lassar (184) has shown that albuminuria may be produced by exposure of the surface to cold, and the albuminuria of " varnished " animals may belong to this class [Winternitz (23)]. Other

experiments of Lassar's, in which he produced nephritis by rubbing croton oil and petroleum into the skin, are scarcely examples of such a connection as we are discussing, for irritation of the kidneys may be set up by the absorption of certain substances without the intermediary of changes in the skin and formation of local decomposition products. Despite these results of experiments on animals, clinical experience provides very few undoubted instances of nephritis depending upon skin disease.

2. Clinical Facts.

(*a*) *Skin Diseases.*

From the extraordinary frequency of nephritis, and the obscure origin of the majority of cases, it is not justifiable in an individual instance to assume when the two conditions coexist that the nephritis is directly attributable to the skin disease, for the latter is so often seen without the complicating kidney disease. One has to bear in mind in such cases that in a skin disease of long standing the treatment has involved the use of internal and external remedies, to whose absorption the kidneys have not been wholly indifferent, a point which makes it difficult to apportion correctly the blame attaching to the skin disease. Had attention been paid to this circumstance, a great deal of the work on albuminuria—*e.g.*, in scabies—would have gone unpublished (*cf.* Glaserfeld, Hübner (184)]. In other skin diseases it is certainly not a question of the effect of skin changes upon the kidney, but some toxine circulating which damages both the skin and the kidneys, as in the acute exanthems, measles, variola, scarlet fever, in syphilis, etc., and perhaps also in pemphigus and in the hæmorrhagic diatheses generally. Transient albuminuria, too, may be much more common in healthy men whose kidneys are presumably sound than was formerly supposed.

The whole question is very complex and beset with uncertainties. In a limited number of cases the connection seems beyond dispute. Leyden (185) many years ago reported a few cases of nephritis for which he could discover no cause beyond a long-standing eczema. Similar cases have been published by Liveing, Bruhns, Bluhm, and Pechkranz (186). One particularly interesting case is that of Salvioli's (187), in which nephritis appeared in a patient with impetiginous eczema on the forty-third day. In a case of amyloid kidney Lecorché and Talamon could not find any other cause but chronic eczema. Other skin diseases in which albuminuria often occurs are pityriasis rubra [Cesarini (189)], dermatitis exfoliativa [Wilson-Brocq], pemphigus vegetans [Perrin, Vilenski (190)]. In dermatitis herpetiformis, on the other hand, these authors have made the very far-fetched suggestion that the nephritis is the primary condition, and that the skin disease is the result of renal insufficiency.

Müller (191) has described the occurrence of albuminuria in impetigo contagiosa, and Dohrn and Wilms in cases of severe burns.

There are certainly cases, too, of skin disease associated with ulcera-

tion in which albuminuria is present. The absorption of the products of bacterial metabolism and decomposition may here form the connecting-link between the two processes. The albuminuria of urticaria and acute circumscribed œdema falls into a separate class, since it is not unreasonable to suppose that the same vasomotor disturbance which produces in the skin urticaria and œdema may in the kidney bring about albuminuria [Senator, Rubens (192)].

(*b*) *Syphilis.*

The literature of syphilitic inflammations of the kidney is very voluminous. It has long been proved that gummatous changes in the kidney often cause albuminuria. The only disputed point has been whether a recent syphilitic infection can set up in the secondary stage a specific nephritis. It is certainly a very rare event. In spite of the scepticism of Welander (193) and Senator (194), some attention must be paid to the careful work of Karvonen (195), who investigated a group of cases, and proved definitely the existence of a temporary nephritis directly after the appearance of secondary symptoms, and before the exhibition of mercury, the course of the renal symptoms proceeding parallel with the progress of the disease, and the albuminuria disappearing under mercurial treatment. However, the whole question is fully dealt with in the works of Senator, Welander, Karvonen and Schwimmer (196). A slight transient febrile albuminuria is evidently by no means rare in secondary syphilis [Petersen (197)], and occasionally instances are seen of very severe nephritis with great œdema, and an amount of albuminuria such as occurs in no other form. Descoust (198) describes one case where at the outset the urine had a specific gravity of 1060, and contained 110 grammes of albumin in 800 c.c. (13·7 per cent.). In the deposit were numerous epithelial casts and crystals of leucin and tyrosin, but no red or white blood-corpuscles. The albumin disappeared from the urine under mercurial treatment.

A similar case has just been published by Hoffmann and Salkowski (199). The albumin at the onset amounted to 8·3 per cent., the specific gravity being 1057. After the urine had stood for several days in the cold, a fine amorphous deposit of albumin appeared, its composition being midway between a globulin and albumin. After allowing the sediment to stand for a few hours in a weak alkaline solution, it became soluble again in water—a phenomenon, according to Salkowski, not hitherto described. The administration of mercury cured the albuminuria. Microscopically, the deposit was only scanty. It consisted of a few leucocytes and red cells, with isolated epithelial and hyaline casts.

From the observations recorded in acute syphilitic nephritis, there seems to be some peculiar relation between the amount of albumin and the scantiness of the sediment, while there is less blood in the urine than in any other form of acute nephritis. However, other observers report differently. A profuse rash usually breaks out.

Fürbringer and Welander (220) have raised the objection that the administration of mercury in syphilis produces casts in the urine, and

often leads to a slight albuminuria, which tends to disappear spontaneously. This albuminuria Fürbringer found in 8 per cent. of cases of syphilis, while Welander, finding casts in the urine to some extent in 57·5 per cent. of cases, puts the percentage as high as 12·5 per cent. Ott (201) has noticed in the cure by salicylate of mercury that the urine contains an appreciable amount of nucleo-albumin.

(*c*) *Gonorrhœa.*

In France considerable attention has been drawn to the frequency of renal albuminuria in gonorrhœa [Balzer, Souplet (202)], although, perhaps, the amount of serum due to suppuration in the urethra has not been sufficiently taken into consideration ; and this seems to be of some moment according to Goldberg (203), who in 12 per cent. of patients with gonorrhœa observed albuminuria, even after deducting the share of albumin attributable to the pus cells. Of these 12 per cent., he inferred that 2 or 3 per cent. were suffering from a consecutive, and the remainder from a metastatic, nephritis. Goldberg further suggested that the balsams used in treatment might be responsible in some degree for gonorrhœal nephritis.

B.—EFFECT OF KIDNEY DISEASES ON THE SKIN.

The texture of the skin is often altered in diseases of the kidney, according to the stage of the disease, at one time being œdematous and swollen, at another becoming dry and harsh. The tendency of nephritic patients to develop skin diseases is well known. Merck (204) quotes especially pruritus, urticaria, erythema, and eczema, particularly a papular form which he distinguishes as a specific variety from its onset and tendency to spontaneous cure. See also Veich (263).

We have observed a remarkable phenomenon occurring just before death, the skin becoming covered with sweat, which deposited a thick layer of crystals of urea ; according to Djoritch (205), this sweat is mixed with a considerable amount of sebum.

VIII.—DISEASES OF THE SKIN AND DIABETES.

A.—SKIN DISEASES AS THE CAUSE OF GLYCOSURIA.

The connections between the skin and the pancreas are too remote to permit a distinct indictment of any skin disease as an actual cause of glycosuria. Syphilis, perhaps, by causing endarteritis of the pancreatic vessels, might lead to diabetes, but both diabetes and syphilis are, however, so rife that it is impossible in any given instance to establish any close connection between them. Cases of glycosuria are reported as having been cured by mercury and iodides [von Noorden (206)].

B.—SKIN DISEASES AND GLYCOSURIA FROM A COMMON CAUSE.

Many authorities regard psoriasis and diabetes as both owing their origin to a common " vasomotor neurosis " [Gross, Strauss, Grube]. Nagelschmidt (207) has demonstrated alimentary glycosuria in eight cases of psoriasis out of twenty-five (*i.e.*, 32 per cent.), but this must have been to some extent a matter of chance (one might quote many cases of psoriasis, for instance, in alcoholics), for Pick, working in Neisser's clinic, only found it in 4 per cent. out of fifty cases of psoriasis—*i.e.*, no more than in many other skin diseases.

C.—SKIN DISEASES AS THE RESULT OF DIABETES.

Diabetes, on the other hand, plays a very important part in the production of skin lesions ; in fact, no constitutional disease can at all compare with it in this respect.

Excluding furunculosis, Kaposi (209) cites the following conditions :

1. Pruritus cutaneus, general or localized.
2. Urticaria chronica, especially papulosa.
3. Acne cachecticorum.
4. Eczema, particularly of the genitals ; balanitis, set up by local decomposition of urine containing sugar.
5. Paronychia diabetica (including loss of hair).
6. Diabetic gangrene (including one case described as gangræna diabetica bullosa serpiginosa).

And to these many more groups might be added.

1. Increased Vulnerability of the Skin.

It is universally admitted that diabetes increases the vulnerability of the skin, tends to promote suppuration in simple inflammation, and delays healing. The same factors probably predispose to simple and seborrhœic eczema, boils, carbuncles, and phlegmon, and, though more doubtfully, perhaps to psoriasis.

2. Degenerative Changes.

There is a second group in which diabetes shows its characteristic nature in causing premature degenerative and senile changes, including those arising from neuritis : scanty perspiration, thinning and wrinkling of the skin, baldness, thinning of the nails, and Dupuytren's contraction.

3. Vascular Degenerations.

Foremost among these are the whole class of diabetic gangrenes. In all of such lesions the vessels are found to be unduly atheromatous, whether examined by the Röntgen rays or in the limb itself after amputation. The rarity of gangrene of the penis forms an exception ; it is due to infection and phlegmonous inflammation, and not to arterio-sclerosis.

4. Xanthoma.

This complication forms a class by itself, and is of very rare occurrence if only cases with extensive xanthoma of the eyes are admitted, but is quite common if one includes those cases in which a few minute xanthomatous masses are found in the skin. Most authors—recently, at any rate—distinguish a type peculiar to diabetes, and regard it as a different affection from ordinary xanthoma. There is a remarkable connection between the course of diabetic xanthoma and the glycosuria, while, moreover, it may occur in pentosuria [Colombini (210)].

5. Destruction of Blood Pigment.

Abnormal Changes in the Skin from the Breaking Down of Blood Pigment in Diabetes.

(*a*) *Xanthosis.*—There is a condition which we have seen in many patients (usually young adults), with severe diabetes, in which the hands, the soles of the feet, the forearms, and sometimes the entire skin, acquire a peculiar tint that has not been previously described. To this we have given the name " xanthosis." The colour varies from a light canary to a deep orange yellow ; it changes readily in its intensity, and exhibits a remarkable relation to the degree of acetonuria. It appears to be somewhat similar to the pigmentation of the hands and feet observed by Sibirski (211) in severe cases of typhoid, which he attributes to a breaking down of hæmoglobin. Our cases of xanthosis have run parallel with the amount of acidosis, so that as the acetone is diminished the pigmentation may disappear within a few weeks.

(*b*) *Diabetic Bronzing.*—Perhaps xanthosis should be regarded as an early stage in the development of diabetic bronzing [Hanot, Chauffard]. This affection has been shown by many observers (213) to be due to the deposition in the skin of an iron-containing pigment (hæmosiderin), one which is almost iron-free, and hæmofuchsin, which is entirely free from iron.

The condition is not peculiar to diabetes ; at any rate, it cannot be sharply differentiated from von Recklinghausen's hæmochromatosis. Osler and Hess suggest that the primary change is some unknown error of metabolism from which the characteristic symptoms of the disease proceed. It is, at all events, worth noting that hæmoglobinuria has been described during the course of the disease by Hess and ourselves, and in each case has been associated with lipæmia.

6. Therapeutics.

It is an old observation, borne out by practical experience, that most of the skin complications of diabetes depend upon the presence of sugar in the blood, and that a rational treatment of the glycosuria is more effectual than the usual remedies applied to the skin. This holds good particularly in eczema, pruritus, disordered perspiration, xanthoma, and trophic lesions of all sorts; but anti-diabetic treatment is entirely thrown away on inflammatory conditions and gangrene.

It is not enough, however, merely to render the urine free from sugar: the withdrawal or restriction of carbohydrates in the diet must be persevered with until the sugar in the blood is reduced to normal. As Liefman (76) recently found in von Noorden's clinic, hyperglycæmia often outlasts the glycosuria by some time, and yields only if the withdrawal of carbohydrates is persisted in: a point that has hitherto been somewhat neglected, and explains a great many of the disappointing results of diabetic treatment.

IX.—GOUT AND SKIN CONDITIONS.

With the question of the relationship between uric-acid metabolism and skin disease we enter a province in which theories and the wildest fancies have run riot. It is not as if they had been suggested by any clinical basis; theories as to "diathesis" can dispense with a foundation altogether! All the speculations on this subject, based on the most flimsy of facts, may be consigned to oblivion, for they offer no scientific foothold, and conceal only a quagmire of ignorant conjecture. Sound work has been done, however, by Gigot-Suard (215) and Quinquaud (216), dealing with the experimental skin diseases produced in animals by overfeeding and by the injection of uric acid: the former claims to have produced psoriasis, pityriasis, prurigo, lichen, and ecthyma; while the latter, by injecting on two occasions 0·15 to 2·02 grammes of uric acid in man, induced the appearance of erythematous patches and blisters, as well as quite atypical rashes. Blaschko submits the objection that these results are the more remarkable since much larger doses combined with overfeeding, both in man and animals (undertaken for other purposes), has given rise to nothing of the kind. In all skin diseases where it has been estimated the output of uric acid has been within normal limits [Lewin (217), Radaeli (36)]. Some statements as to the retention of uric acid bear the stamp of inaccuracy, as does the theory of "an alloxuric origin for eczema," which Tommasoli (218) himself acknowledges to have abandoned, "for, as holds good in any grave charge, uric acid must be acquitted when it is proved to be absent."

The clinical facts on which the theories of a "diathèse dartreuse," an "arthritism," etc., are based are chiefly the undoubted frequency of eczema and psoriasis, coincident with diseases of the joints on the one

hand and asthma on the other ; so remarkable is the frequency of this coincidence that even the total absence of any explanation cannot rob the comprehensive theories of Bazin, Hardy, Brocq, Gaucher, etc. (219) of their foundation. But for the well-known alternation between these affections, not even an adequate clinical explanation is forthcoming.

Among genuine gouty manifestations in the skin may naturally be reckoned the uratic deposits and the resulting inflammations ; further, it is not to be questioned that various trophic changes in the skin of the fingers and the nails are caused by gout ; this is natural in a disease which displays such tendencies to constitutional degeneration. Varices, eczema, punctiform hæmorrhages, abnormal pigmentation, and ulceration of the legs are very common, but they, perhaps, are no more due to the uric-acid diathesis than to the defective circulation, which is also a cause of adiposity. It should not be overlooked that possibly the same constitutional tendencies which predispose to gout may determine the liability to skin affections ; and if one limits the interpretation to such diseases as occur in children who sooner or later actually manifest the gouty diathesis by attacks of gout or uratic deposits, all that remains is perhaps a somewhat greater liability to eczema and psoriasis in gouty subjects. If, however, the theory of a " gouty diathesis " is used as a convenient cloak for inaccurate diagnosis—as is too often the case—the province of gouty dermatoses is considerably extended. In the interests of both general medicine and dermatology, so loose an application of the diagnosis of gout should be done away with, and only those skin diseases should be permitted to assume the title " gouty " whose claims can be sustained by objective symptoms and not by mere tradition.

X.—CHEMICAL CHANGES IN THE SKIN.

1. Albumin.

In this department we find ourselves groping on the outskirts of knowledge, for no chemical facts have been positively proved. We may, perhaps, assume that the differences in reaction to stains which many of the morphological constituents of the skin exhibit in these diseases correspond with chemical changes. Schmidt (202) has shown that in senile changes the elastic fibres of the skin behave abnormally towards certain stains. Unna (221) demonstrated that the elastic fibres normally oxyphile become in this state basophile ; he called the altered substance " elacin," in contradistinction to the normal " elastin." This " elacin " may occur in various degenerative processes in the skin, including atrophy. According to Unna and Krzystalowicz (222), the collagenous tissue shares in the degeneration (formation of collacin and collastin). The extensive changes in the staining reactions of the collagenous and elastic tissues in myxœdema described by Unna are of the greatest interest. Whether, among the recognised skin changes of myxœdema, the actual deposition of mucin takes place has not yet been chemically investigated. Of the chemical

composition of keratohyalin (and eleïdin) very little is known, save that the process of keratinization may represent the converse to that of myxœdema [Ernst, von Dreysel, Oppler (223)].

2. Carbohydrates.

Glycogen has been shown to be normally absent from the skin, but its presence has been demonstrated (Ehrlich's method) in the following diseased conditions : Lupus vulgaris, eczema, intertrigo, syphilomata, pityriasis rubra, herpes iris, polymorphous exudative erythema, and lichen ruber (chiefly in the sweat glands) [Bosellini (224)]; in epitheliomata, papillomata, and condylomata [Lubarsch (264)]. Gierke has demonstrated the presence of glycogen in the outer hair root-sheath, sebaceous glands, and epithelium of the sweat glands of normal skin. Glycogen is not present in the epidermis (265).

3. Fats.

No analyses have been made of the total fat in the skin in individual diseases, such as seborrhœa, etc. Unna (225) shows from microscopic appearances that there is an increase of fat in seborrhœic eczema, but the fallacies of a histological estimate based solely upon the osmic-acid stain for fat have long been deprecated [Rosenfeld]. It is, at any rate, not unreasonable to assume that in seborrhœa the increase of fat in the secretion corresponds to a similar increase in the skin ; at the same time, we cannot be sure, with our present knowledge, that the serum accumulated on the skin—as in seborrhœic eczema—can be accurately separated from the fat itself. The method suggested by Greciet (226) is very problematical. It depends upon Arnozan's (227) observation that the presence of fat arrests the rotation of a piece of camphor floating in water, and according to this method, fat is absent from the secretion in ichthyosis, eczema, and seborrhœa ! Although it does not deal with quantitative results, the work of Linser (228) upon the qualitative analyses of skin secretions is of the greatest value. His exhaustive research was carried out upon the normal sebum of the skin (collected by rubbing the surface with petroleum ether) and upon the sebaceous material of dermoids, etc., with a view to determining the melting-point, the acid, the saponification number, and the fatty acids and cholesterin in the ether extract. He used as a control the ether extracts of various horny substances such as cow's horn and horse's hoofs. He thus found that the constituents of sebum soluble in ether were, as a whole, included in two classes : first, the secretion of the sebaceous glands, which contains little cholesterin and substances of similar composition ; secondly, the horny materials soluble in ether and rich in cholesterin. In the sebaceous secretion of ichthyosis and psoriasis, in comedones, seborrhœa sicca, and seborrhœa oleosa, he found just the same variations between one disease and another as between any one of them and normal sebum. In psoriasis, ichthyosis, and comedones, the cholesterin in the extract was very abundant, and

exceeded the amount of fat obtained from the horny substances; seborrhœa oleosa, on the other hand, gave an ether extract poorer in cholesterin, but much richer in free fatty acids, notably oleic acid.

Linser tabulated his results as follows:

Substance.	*Amount in Gm.*	*Melting-point.*	*Acid Number.*	*Saponification Number.*	*Iodine Number.*		*Unsaponified Part.*	
					Total Ether Extracts.	Fatty Acids.	Per Cent. of Ether Extract	Cholesterin.
Normal sebum ..	12·0	33°–36°	3·4–7·9	117–140	54–67	36–44	40–45	+
Ichthyosis ..	1·4	40°	5·3	94	62	41	50	+++
Psoriasis ..	1·3	40°–41°	4·7	81	59	—	50	++
Comedones ..	1·0	39°	19·3	109	—	54	40–50	++
Seborrhœa sicca	1·2	36°–38°	51·9	154	—	57	—	+
Seborrhœa oleosa	2·0	32°	77·6	183	—	67	20	Trace

\+ Small amount. ++ Large amount. +++ Very large amount.

This interesting line of research is worth continuing, as it promises to throw fresh light upon the diseases of the skin associated with secretion.

Knöpfelmacher has investigated the origin of sclerema neonatorum (229), and suggests that it is due to a solidification of the skin-fat in children, a process which is favoured by the fact that the fat of new-born infants contains much less olein than that of adults [Langer (230), Knöpfelmacher].

Rosenfeld's admirable researches upon the effect of diet on the fat-secretion of the skin cannot be quoted at length, but they contain a wealth of information obtained by methods leaving no room for error, or opportunity for carping criticism (267).[1]

4. Salts.

Deposition of calcium salts in the skin occurs fairly commonly in the calcification of epithelial tumours, cysts, new growths, etc. There is also a peculiar condition whose histological and clinical characters are very different, in which, just as in gout, salt concretions are deposited in the skin and subcutaneous tissues, leading to acute inflammation. These concretions, however, contain no trace of uric acid, being formed entirely of calcium phosphate and carbonate. The histological appearances are those of gouty tophi. Such cases have been described by Weber, Jeanne, Morell-Lavallée, Riehl, and von Tannenhain (231); while Wildbotz (232) and Lewandowsky (232) have carefully investigated the disease. The chemical analysis of the concretion shows that it contains a small amount of fat and albuminous material, but consists chiefly of phosphate and carbonate of calcium. In Tannenhain's case calcium carbonate was present alone. These cases suggest a line of research similar to that adopted by Soetbeer on the nature of phosphaturia (increase of calcium salts in the urine). In many of his cases it appears

[1] *Zentralbl. f. innere Med.*, 1906, xxvii., 986.

that phosphaturia was present. In the only case in which a quantitative analysis of the calcium salts was made (without reference to a "calcium balance," it is true) the excretion amounted to 0·25, almost above the highest normal limit. Soetbeer advanced the view that when there was an insufficiency of calcium excretion by the bowel, not only the kidneys, but on occasions the skin, might act vicariously. Merck, too, describes a superficial deposit of phosphates on the skin under the term "phosphatidrosis" (223), which he saw accompanying phosphaturia in an eruption looking like a combination of pityriasis versicolor and ichthyosis.

5. Halogens.

Attempts have often been made to prove the presence of bromides and iodides in the secretion of the sebaceous glands in bromide and iodide acne [Adamkiewicz and Guttmann (234)]. As Jarisch has already pointed out, only a limited importance can be attached to the numerous positive results until some quantitative determinations are made, whereby the surplus of bromides and iodides in the various fluids of the body entering into other tissues can be estimated. At any rate, it is probable that excretion does take place by the sebaceous glands [Justus (266)]. Nothing is known about the presence of chlorides in the secretion which Herxheimer first described in chloride acne. It cannot be denied—although the proof is wanting—that the disease may be produced by organic chlorine compounds, which are excreted as chlorides by the sebaceous glands [Lehmann (237)].

6. Pigments.

We have very little knowledge so far of the chemical composition and the conditions attending the formation of the pigments deposited in various diseases of the skin, although of late some work has been done in this direction [Samueli (238), Wolff (239)]. The question chiefly studied at present is whether iron can be discovered microchemically in the various pigments. In the pigment of Addison's disease no iron reaction can be obtained. Hæmosiderin is present in most of the other forms of pigmentation, in the bronzing of diabetes, and vagabonds pigmentation, and the melanin of melanotic sarcoma. Schmidt, however, has proved that the iron reaction forms no criterion of the pigment having been derived from the blood, since it may be absent in both recent and old hæmosiderin deposits. It is an unsolved problem whether abnormal pigmentation in particular diseases is due to metabolic processes in the cells, or is deposited by the blood-stream : a question hitherto only approached from the point of view of histology, so that for the present it is outside our subject.

LITERATURE.

General Summaries—Jesser : Hautanomalien bei inn. Krankheiten. 1893.—Ullmann : Zur Beurteilung von Hautanomalien als Ausdruck von Organstörungen. W. m. W. **1903.** Nr. 3-5. Ueber autotoxin. und alimentäre Dermatosen. W. m. P. **1905.** Nr. 23.

1. Wilms : Pathol. der Verbrennung. G. M. C. **8.** 393. 1901.

2. Rouanet : Untersuch. über das Blut, den Harnstoff und die Temper. des Trippers. J. M. **1895.** H. 2 and 3. Mo. D. **20.** 615. 1895.—Noguès :

Ueber die Temper. beim akuten Tripper. An. g.-u. **1895.** Nr. 5. Mo. D. **21.** 182. 1895.

3. Heller: Die Onychopathol. 6. V. K. D. 277. **1899.**

4. Bedard: Ar. g. m. Janv., 1872. Cited by Billroth.—Billroth: Ueber auffallend niedrige Temperat. bei gewissen Krankheiten des Menschen. Ar. k. C. **6.** 405. 1865.

5. Stüve: Über den respirat. Gaswechsel bei Schilddrüsen-fütterung, bei Morb. Basedowii und bei Diab. mell. A. K. **1896.** (Festschr.).

6. Tendlau: Ueber angeborene und erworbene Atrophia cutis idiopathica. Ar. p. A. **167.** 465. 1902.

7. Quinquaud et Leredde: Notes sur deux cas des Mykosis fongoïde. A. D. S. **4.** 1276. **1893.**

8. Magnus-Levy: Untersuch. zur Schilddrüsenfrage. Z. M. **33.** 269. 1897. Ueber Myxodem. Z. M. **52.** 201. 1904.—Salomon: Gaswechseluntersuch. bei Morb. Basedowii und Akromegalie. B. k. W. **1902.**—R. Stüve: Nr. 5.

9. Jeanselme: Coexistence du goître exophthal. et de la sclérodermie. Se. m. **14.** 357. 1894.—Leube: Basedowsche Krankheit. 1893.—Kahler: Ueber die Erweiterung des Symptomenkomplexes der Basedow. Krankheit. P. W. **13.** 313. 1888.—Ditisheim: Ueber Morb. Basedowii. Diss. Basel, 1895.—Krieger: Ein Fall von Sklerodermie nach vorausgegang. Morb. Basedowii. Mü. m. W. **50.** 1772. 1903.

10. Schubiger: Ueber Sklerodaktylie. Mo. D. **24.** 397. 1897.

11. Singer: Zur Path. der Sklerodermie. B. k. W. **32.** 226. 1895.—Hektoen: Ein Fall von Scleroderma diffusum. C. a. P. **8.** 673. 1897.

12. Weber: Ein Fall von Sklerodermie erfolgreich behandelt mit Extr. thyr. N. Y. M. **9.** 545. 1897.—Porter: Diffuse Sclerodermia. B. M. J. 893. I. **1901.**

13. Volhard: Ueber chron. Dystrophien und Trophoneurosen der Haut im Anschluss an kasuist. Mitteil. Mü. m. W. **50.** 1108. 1903.

14. Winfield and van Cott: Etiology of Congenital Ichthyosis. J. C. D. 1897. XV. 373.

15. Weiss: Adipositas dolorosa. Ctb. G. M. C. **7.** 56. 1904.

16. Byron Bramwell: B. J. D. **6.** 1894. Mo. D. **19.** 447. 1894; also Brit. Med. Assoc. Meeting. 1898.

17. Dill: Five Cases of Skin Diseases treated by Thyroid Gland. L. **72.** 19. 1894.—Zum Busch: Die Schilddrüsenbehandl. bei Myxödem und bei verschied. Hautkrankh. D. Zt. 2. 433. 1895.

18. Abraham: Cases of Dis. of the Skin treated with Thyroid Gland. L. 94. I. 1894.—Thibierge: Le traitement thyreoidien du psoriasis. A. D. S. **6.** 760. 1895.—Zarubin: Zur Frage von der Behandl. der Hautkrankh. mit den Schilddrüsenpräparaten. (Literature.) Ar. D. S. **37.** 421. 1896.—Scatchard: Case of Pityriasis Rubra treated with Thyroid Tabloids. B. M. J. 695. **1895.**

19. Ewald: Ueber Thyreoidinbehandl. der Psoriasis. B. k. W. **38.** 147. 1901. (Literature.) Krankh. der Schilddrüse, Myxödem und Kretinismus. Nothnagel's Handb. **22.** 1896.—Organotherapeutisches. T. G. **1.** 85. 1899.—Ueber therap. Anwendung der Schilddrüsenpräparate. V. C. M. 101. **1896.**

20. Saalfeld: Ein Beitr. zur Oophorinbehandl. B. k. W. **35.** 283. 1898.—Sottas: Dermat. prurigineuse consée. à la castration ovarienne guérie. par l'opothér. A. D. S. **3.** 372. 1902.

21. Edenbuizen: Beitr. zur Physiol. der Haut. Z. r. M. **17.** 1863.

22. Lassar: Ueber den Zusammenhang von Hautresorp. und Albuminurie. Ar. p. A. **77.** 157. 1879.

23. Krieger: Untersuch. über die Entstehung von entzündl. und fieberhaften Krankh. Z. B. **5.** 476. 1869.—Laschkewitsch: Temperaturerniedrigung bei Hautperspiration. Ar. A. P. **4.** 61. 1868; also Ar. M. **6.**—Lomikowsky: Cause des altérations surven. dans les organes internes chez les animaux par suite de la suspension de la perspiration cutanée. J. A. P. **14.** 468. 1878.—Winternitz: Über Abkühlung und Firnissung. Ar. P. P. **33.** 286. 1894.

24. Babák: Ueber die Wärmeregulation nach der Firnissung der Haut. Ar. P. M. **108.** 389. 1905. See also Unna: Ueber die insensible Perspiration der Haut. V. C. M. **1890.**

25. Senator: Wie wirkt das Firnissen der Haut bei Menschen. Ar. p. A. **70.** 182. 1877. Z. M. **24.** 184. 1894.

26. Levy-Dorn: Wie wirkt das Firnissen der Haut beim Menschen? Z. M.

24. 419. 1894. Über den Einfluss des Firnissens der Haut beim Menschen. D. A. 221. **1894.** Ueber den Absonderungsdruck der Schweissdrüsen und über das Firnissen der Haut. Z. M. **23.** 309. 1893.

27. UNNA: Ueber die Perakeratosen im allge. und eine neue Form derselben. Mo. D. **10.** 409. 1890.

28. QUINCKE: Ueber die Perspiration bei Hautkranken. D. Zt. **1.** 330. 1894.

29. BIELING: Ueber die Perspiration beim universellen Ekzem. Diss. Kiel. 1894.

30. REISS: Sur la perspiration de la peau. A. D. S. **9.** 497. 1898.

31. LEICHTENSTERN: Ein mittels Schilddrüseninjektion und Fütterung erfolgreich behandelter Fall von Myxœdema operativum. D. m. W. **19.** 1333. 1893.—PEIPER: Über die Perspir. insensib. unter normalen und pathol. Verhält. 1888.

32. JANSSEN: Die Hautperspir. beim gesunden Menschen und bei Nephritikern. D. Ar. M. **33.** 334. 1883.

33. SCHWENKENBECHER: Ueber die Aussch. des Wassers durch die Haut von Gesunden und Kranken. D. Ar. M. **79.** 29. 1904.

34. LINSER AND SCHMIDT: Ueber den Stoffw. bei Hyperthermie. D. Ar. M. **79.** 514. 1904.

35. STÜVE: Stoffwechseluntersuch. betreffend einen Fall von Pemphigus vegetans. Ar. D. S. **36.** 191. 1896; also A. K. 38. 1896.

36. RADAELI: Ricerche sul ricambio materiale in un caso di Lichen ruber planus. Gi. M. v. 416. 1901; Pemfigo e pemfigoidi. Ibid. **38.** 349. 1903.

37. JAKOVLEFF: Stickstoffwech. der Syphil. in der Eruptionsperiode. Diss. St. Peters. 1897.—RADAELI: Ricerche sul ricambio materiale nella sifilide recente. S. **3.** 263. 1900; Ricerche sul ricambio materiale nella sifilide recente. Gi. M. v. **35.** 412. 1900.—CEDERKREUTZ: Stickstoffwech. in der Frühperiode der Syphilis. 1902. (Literature.)

38. QUINQUAUD: C. r. S. B. **1890.** 729.

39. BURGSDORF: Grundlage der Lehre von der Pityriasis rubra und exper. Untersuch. über den Stoffw. N-haltiger Produkte bei dieser Krankheit. B. k. W. **40.** 151. 1903.

40. GROBER: Ueber den wechselnden Rhodangeh. des Speichels, seine Ursachen beim gesunden und kranken Menschen. Ar. M. **69.** 243. 1901.—JOSEPH: Ueber die Rhodanaussch. im Speichel Syphilitischer. Ar. D. S. **70.** 49. 1904.—MEUSE: Ueber die Schwankungen des Rhodankaliumgeh. im Speichel. A. T. S. **1903.** Nr. 7. C. i. M. **24.** 1217. 1903.

41. MAYER: Ueber die Menge des Rhodans im menschl. Speichel und Harn bei Gesunden und in einigen Krankheitszust. D. Ar. M. **79.** 209. 1904.

42. BOUCHARD, cit. by TOUTON: VI. V. k. D. P. 109.

43. BARTHELEMY: Aetiol. und Behandl. der Akne. 1896. Mo. D. **9.** 1888. See also TOUTON: (42).

44. BLASCHKO: Autointox. und Hautkrankh. B. K. **4.** 87.

45. COMBY, cit. by BLASCHKO: V. b. M. 17 Okt., 1894.

46. FUNK AND GRUNDZACH: Ueber Urticaria infantum. Mo. D. **18.**

47. MITOUR: Nature et le traitem. de la dyspep. accompagnée d'acné. Thèse de Par. **1896.**

48. MILLON: Zur Aetiol. der gewöhnlichen Dermatosen des Kindesalters. M. i. 15. III. 1894.

49. LASSAR: Ernährungsther. bei Hautkrankh. D. Zt. **11.** 197. 1904.

50. QUINCKE: Ueber akutes umschriebenes Hautödem. Mo. D. **1882.**—WEINTRAUD: Gastrointest. Autointoxik. Er. P. **4.** 1. 1899.

51. ALBU: Ueber die Autointoxik. des Intestinaltraktus. 92. **1895.**

52. SINGER: Ueber den sichtbaren Ausdruck und die Bekämpfung der gesteigerten Darmfäulnis. W. k. W. **7.** 37. 1894. Also Krit. Bemerkungen zur Lehre von der Autointoxikation. W. m. P. 28 März, 1897.

53. FREUND: Ueber Autointoxikationserytheme. W. k. W. **7.** 39. 1894.

54. HEVEROCH: Ueber das ursächl. Verhält. der Darmfäulnis zu einigen Dermatosen. W. k. W. **47.** 2029. 1897.

55. JANOWSKY: III. I. D. C. 1896. Discussion. A. D. S. 1108. 1896.

56. GAUCHER ET DESMOULIÈRE: Des troubles de la nutrition et de l'élimination urinaire dans le psoriasis. J. P. P. g. **6.** 703. 1904.

57. JADASSOHN: Die Toxikodermien. D. K. 148. 1902.

58. Lassar: Praktische Notiz. D. Zt. **4.** 150. 1897. T. G. 1899.
59. Brocq: P. m. **7.** 45. 1899. For Literature cf. Hedrich: Das Levuretin (eine völlig reine Trockenhefe) und die Saccharomykotherapie (Hefekur). D. Aerztezt. 49. **1904.**
60. Roos u. Hinsberg: Eine ther. wirksame Substanz aus der Hefe, Cerolin, Fettsubstanz der Hefe. Mü. m. W. **50.** 1196. 1903.—Quincke: K. i. M. 193. **1898.** Discussion.
61. Koziczkowsky: Ueber den Einfl. von Diät und Hefekuren auf im Urin erscheinende enterogene Fäulnisprod. Z. M. **57.** 413. 1905.
62. Bendix: Zur Aetiol. der Urtikaria im Kindesalter. D. m. W. **29.** 105. V. 1903.
63. Lewin: Berl. Dermat. Ges. 3 December, 1897.—v. Leyden: Ueber das erste Stadium des Morb. Brightii und die akute oder frische Nephritis. Z. M. **3.** 161. 1881.
64. Unna: Über allge. Pathol. der Haut. Mo. D. **11.** 491. 1890.—Berliner: Aetiol. und Ther. der Urtikaria. D. Zt. **2.** 235. 1895.—Jarisch: Die Hautkrankh. in Nothnagel's Spez. Path. und Ther. **24.** 1900.—Lassar: Ernährungsther. bei Hautkrankh. D. Zt. **11.** 197. 1904.
65. Philippson: Ricerche sperim. sule Urticaria. Gi. M. v. 1899.—Philippson: Ueber das flüchtige Reizödem der Haut und sein klin. Vorkommen. Ar. D. S. **65.** 387. 1903.
66. Török u. Hari: Über die Pathogen. der Urtikaria. Ar. D. S. **65.** 21. 1903.
67. Török u. Vas: Ueber den Eiweissgeh. des Inhaltes von Hautblasen. Festschr. für Kaposi. 439. 1900. Cf. Török: Ueber das Wesen der sog. Angioneurosen der Haut. Ar. D. S. **53.** 243. 1900.
68. Frisko: Sulle dermat. nelle autointossicazione e nelle intissicazione bacteriche sperim. Gi. M. v. **32.** 545. 1897.
69. Lombroso: Die Lehre von der Pellagru. 1898.
70. Babes et Manicatide: Sur certaines substances specifiques produites par l'organisme des pellagreux. C. r. A. S. Juill., 1900.
71. Brocq: Le régime aliment. dans les dermatoses. Festschr. für Lewin. 10. 1896.
72. Jarisch: Die Hautkrankh. in Nothnagel's Spez. Pathol. u. Ther. **24.** 447. 1900.
73. Veiel: Ther. der Akne. 6 V. k. D. 173. 1896.
74. Neisser: In the Discussion on Acne. 6. V. k. D. 162. 1896.
75. Guinsbourg: Vegetab. Diät bei chron. Furunkulose. An. T. III. Nr. 6. 1903. Mo. D. **37.** 283. 1903. Vegetar. Diät gegen chron. Furunkulose. D. Zt. **10.** 39. 1903.
76. Liefmann: Unpublished: will appear in Be. P. P.
77. Borri: L'acidità urin. in rapporto ad alcune dermopatie. Gi. M. v. **37.** 463. 1902.
78. Wickham: A. D. S. **4.** 1183. 1893.
79. Desgrez et Ayrignac: Étude des échanges nutritifs dans les dermatoses. J. P. P. g. **7.** 1905.
80. v. Jaksch: Ueber die Verteil. der stickstoffhaltigen Substanz im Harn des kranken Menschen. Z. M. **47.** 1. 1902. Weitere Mitteil. über die Verteilung der stickstoffhalt. Substanz im Harn. Ibid. **50.** 167. 1903.
81. Joseph: Ueber akutes umschriebenes Hautödem. B. k. W. **27.** 77. 1890.—Roques: Troubles vasomot. à forme d'urticaire chez un malade atteint d'hémoglob. paroxystique a frigore. A. D. S. **9.** 412. 1898.—Wende: Acute Circumscribed Œdema associated with Hæmoglobinuria. J. C. D. **1899.** Ref. A. D. S. **10.** 918. 1899.
82. Hoppe-Seyler: Ueber die Veränderungen des Blutes bei Verbrennungen der Haut. Z. p. C. **5.** 1. 1881; also Nachträgl. Bemerkungen über die Veränderungen des Blutes bei Verbrennungen der Haut. Ibid. **5.** 344. 1881.
83. Schultze: Ein heizbarer Objekttisch und seine Verwendung bei Untersuch. des Blutes. Ar. m. A. **1.** 1. 1865.
84. v. Lesser: Ueber die Todesursachen nach Verbrennungen. Ar. p. A. **79.** 248. 1880.
85. Dohrn: D. Z. C. **60.**
86. Lichtheim: Period. Hæmoglobinurie. Vo. s. V. 2. 1147. No. 134.
87. Anderson: Hydroa Æstivale in Two Brothers complicated with the Pre-

sence of Hæmatoporphyrin in the Urine. B. J. D. **1898.** S. J. **1897.** Mo. D. **16.** 160. 1898.

88. Nagelschmidt: Psoriasis und Glycosurie. Diss. Berl. 1900.

89. Surveyor: A New Disease with a Specific Urinary Reaction. L. **78.** 397. 1900.—Chatinière: Expér. sur la toxicité de l'urine des lépreux. A. D. S. **6.** 204. 1895.

90. Calderone: Tossicità dell urina e dell sangue del leprosi. Gi. M. v. **32.** 569. 1897.

91. Fisichella: Sulla tossicità dell urina dei leprosi. R. M. 350. 1893.

92. Carrière et Gilbert: Toxicité urin. dans la mal. de Werlhof. A. D. S. **8.** 796. 1897.

93. Pini: Ricerche chim. e speriment. in un caso di pemphigus veg. Gi. M. v. **33.** 354. 1898.

94. Oro e Mosca: Contrib. allo studio della psoriasi. Ibid. **1902.** A. D. S. **4.** 270. 1903.

95. Colombini: Tossicità urin. in alcune dermatosi. Gi. M. v. **32.** 230. 1897.

96. Griffith: Ptomaine extraite des urines dans l'eczéma. C. r. S. B. 116. 1205. **1893.**

97. Tête et Vandame, cit. by Hallopeau: Toxines en dermatologie. A. D. S. **8.** 854. 1897.

98. Soual: Sur la toxicité urin. et la perméabilité rénale dans la syphilis. J. M. **13.** 75. 1901.

99. Catiano: Zur Theorie der primären Todesursache bei Verbrennungen. Ar. p. A. **87.** 345. 1882.

100. Lustgarten: Zur Theorie der primären Todesursache bei Verbrennungen. W. k. W. **4.** 528. 1891.

101. Kijanitzin: Zur Frage nach der Ursache des Todes bei ausgedehnten Hautverbrennungen. Ar. p. A. **131.** 436. 1896.

102. Ajello e Parascondolo: Ptomaine als Ursache des Verbrennungstodes. W. k. W. **9.** 780. 1896.

103. Reiss: Pathogen. der Verbrennung. Ar. D. S. **25.** 141. 1893.

104. Spiegler: Stud. des Verbrennungstodes. W. m. B. **19.** 259. 1896.

105. Spiegler u. Fränkel: Zur Aetiol. des Verbrennungstodes. W. m. B. **20.** 75. 1897.

106. Weidenfeld: Ueber den Verbrennungstod. Ar. D. S. **61.** 33. 1902.

107. Scholz: Über die Ursache des Todes bei Verbrennungen und Verbrühungen. Mü. m. W. **47.** 152. 1900.

108. Soual: Sur l'augment. du rapp. de chlorures à l'urée dans les urines des syphil. J. M. **13.** 79. 1901.

109. Grosz: Ueber Beziehungen einiger Dermatosen zum Gesamtorganismus. W. k. W. **12.** 211. 1899.

110. Jacquet et Portes: Troubles du chimisme du sanguin et urin. dans la pelade. A. D. S. **2.** 286. 1901; also La viciation hemourinaire dans la pelade. J. D. S. **2.** 322. 1901; cf. also Jacquet: Nature et traitement de la pelade. A. D. S. **1.** 584. 1900.

111. Campana e Condelli: Clinica dermosifilopath. della reg. univ. di Roma. 1903. H. 3.

112. Soetbeer: Ueber Phosphaturie. Ja. K. **56.** 1. 1902.

113. Schlesinger: Ueber die Beeinflussung der Blut- und Serumdichte durch Veränderung der Haut und durch externe Medikationen. Ar. p. A. **130.** 145. 1892.

114. Baradue: Des causes de la mort à la suite des crûtures superficielles. 1862.

115. Tappeiner: Ueber Veränderung des Blutes und der Muskeln nach ausgedehnter Hautverbrennung. C. m. W. **19.** 385. 1881.

116. Hock: Ueber Pathogen. des Verbrennungstodes. W. m. W. **43.** 737. 1893; also Wien. derm. Ges. 11 Jan., 1893.

117. Valerio: L'istotonia, la densità, l'alcalinità e l'emoglobina del sangue dei sifilitici in rapporto coi chloruri avanti e durante la cura mercuriale. Gi. M. v. **31.** 437. 1896. See also Gi. M. v. **31.** 531. 1896.

118. Verrotti: Ematologia della sifilide con speciale riguardo alla diag. delle lesioni chir. di dubia natura. Gi. i. S. **9, 10.** 1900.

119. Dacco: Ricerche ematol. in alcun dermatosi. Gi. M. v. **38.** 405. 1903.
120. Winiarski: Blutuntersuch. bei der Lepra. St. P. **17.** 365. 1892.
121. Okamura: Ueber Blutbefunde bei Xeroderma pigmentosum. Ar. D. S. **51.** 87. 1900.
122. Kaposi: Sitzung der K. K. Gesellsch. der Aerzte in Wien. 27 Jan., 1893.
123. Jourdanet: Pityriasis rubra chron. gravis. A. D. S. **1.** 1067. 1900.
124. Neumann: S. W. D. 9 März, 1892.
125. Zelenew: Quantité d'hémoglob. des globules blancs et rouges chez les psoriasiques. J. mil. Ref. A. D. S. **5.** 880. 1894.
126. Giorgi: Ricerche ematol. nella blenorragi. C. M. i. **1903.** Nr. 8. Ref. F. h. **1.** 171. 1904. See also Eugenio: Ricerche ematol. nella blenorrhagia. C. M. i. **1903.** Nr. 7.
127. Essertau: L'étude micros. du sang et du pus dans l'urétrite blenorrhagique. Thèse de Bordeaux. 1902, 1903. Nr. 54.
128. Ponfik: Ueber die plötzl. Todesfälle nach schweren Verbrennungen. B. k. W. **14.** 672. 1877.—Lesser: Ueber Todesursachen bei Verbrennungen. Ar. p. A. **79.** 248. 1880.—Silbermann: Über die Krankheitserschein. und Ursachen des raschen Todes nach schweren Hautverbrennungen. Ar. p. A. **119.** 488. 1890.—Welti: Ueber die Todesursache nach Hautverbren. Be. A. P. **4.** 519. 1889.—See also Kundrat, S. W. D. **11.** 1. 1893.—Salvioli: Ueber die Todesursachen nach Verbrennung. Ar. p. A. **125.** 364. 1891.—Klebs: Handb. der pathol. Anat. 1868. W. J. **16.** 37. 1868.—Bieganski: Ueber die Blutveränderung infolge von Syphilis und Quecksilber. P. L. **19.** 1891. Nr. 29, 30, 31. Also, Ueber die Veränderungen des Blutes unter dem Einfl. von Syph. und pharmakol. Gaben von Quecksilberpräp. Ar. D. S. **24.** 43. 1892.
129. Wilbuszewicz: De l'infl. des préparat. mercur. sur le richesse du sang en glob. rouges et en glob. blanchs. Ar. P. **6.** 509. 1874.—Ricord: Traité prat. des mal. vénéréennes. 1838.—Gaillard: De l'action du mercure sur le sang chez les syphil. et les anémiques. Ga. H. Nr. 74. **1885.**—Keyes: The Effect of Small Doses of Mercury on the Red Blood-Corpuscles in Syphilis. A. J. M. S. **1876.**
130. Virchow: Die krankhaften Geschwülste. **2.** 419, 420. 1896.—Jawein: Thèse de St. Pétersb. 1896.—Lezius: Blutveränderung bei der Anämie der Syphilit. 1889.—Konried: Ueber quantit. Veränderungen der Bestandteile des Blutes bei Syphilis. I. D. C. Wien. 1892.—Reiss: Ueber die im Verlauf der Syphilis vorkom. Blutveränder. in Bezug auf die Ther. Ar. D. S. **32.** 207. 1895.—Dehio: Blutuntersuch. bei der durch Syphilis bedingten Anämie. St. P. **16.** 1. 1891.—Dacco: Ematol. della sifilide. Gi. M. v. **4.** 407. 1892.—D'Amore: Hämochrom. und Spektrosk. als diagnos. Hilfsmittel und Kontrolle der therap. Erfolge der Jod-Quecksilberbeh. I. R. **1892.** Nr. 25.—Radaeli: Sul modo di compertarsi dei globul. biarchi nella sifilide. P. June, 1896. Ref. Gi. M. v. **31.** 530. 1896.—Bieganski: Ueber die Veränder. des Blutes unter dem Einfl. von Syphilis und pharmak. Gaben von Quecksilberpräpar. Ar. D. S. **24.** 43. 1892.—Antse: Des modif. morph. du sang dans la syphilil. Soc. russie de syph. et de derm. 26 Jan., 1891; cf. A. D. S. **2.** 237. 1891.—Loos: Die Anämie bei hered. Syphilis. W. k. W. **5.** 291. 1892.
131. Smirjagin: Die Blutveränder. in der Spätperiode der Syphilis. R. Z. D. **32.** 569. 1901.
132. Oppenheim u. Löwenbach: Blutuntersuch. bei konstitut. Syph. unter dem Einfl. der Quecksilberther. mit besonderer Berücksichtig. des Eisengehalts. D. Ar. M. **71.** 425. 1901.—Sabrazès et Matthis: Note sur l'état du sang dans la syphilis, le tabes et la paral. gén. J. M. **14.** 7. 1902.
133. Stoukovenkoff: De la chloroanémie syphil. et mercurielle. A. D. S. **3.** 924. 1892.
134. Rille: Veränder. des Blutes bei Syph. und einigen Dermatosen. I. D. C. Wien. 1893; also W. k. W. **6.** 155. 1893.
135. Neumann u. Konried: Über die Veränderungen des Blutes infolge des syphil. Prozesses. W. k. W. **6.** 340. 1893.
136. Feuerstein: Ueber die sog. Justus'sche Hämoglobinprobe bei Syphilis. Ar. D. S. **67.** 363. 1903.
137. Vörner: Ueber Blutplättchenbef. im Blute von Syphil. und ihre Bedeutung. D. m. W. **28.** 897. 1902. See Losdorfer: K. k. Ges. der Aerzte Wiens. Sitz. v. 27 April, 1900. W. k. W. **13.** 413. 1900.

138. Samberger: Zur Pathogen. der syphil. Anämie und des syphil. Ikterus. Ar. D. S. **67.** 89. 1903.

139. Justus: Die Differentialdiag. der Syph. mit Hilfe der Hämoglobinbestim. Festschr. f. Kaposi: Ar. D. S. 494. **1900.** Ueber Blutveränderungen durch Syph. und Quecksilber mit besond. Berücksichtig. ihrer diagnos. Verwertung. D. Ar. M. **75.** 1. 1903. Ueber die durch Syph. bedingten Blutveränder. in Hinsicht ihrer diagnos. und therap. Bedeutung. Ar. p. A. **140.** 91. 1895, and **148.** 533. 1897. Other authors quoted by Feuerstein.

140. Jones: On the Justus Blood-test in Syphilis. N. Y. J. **71.** 513. 1900. Cabot and Martin: The Justus Test in Syphilis. B. M. and S. J. 6 Apr., 1899. Ref. Mo. D. **31.** 455. 1900.—Christian and Förster: The Justus Test in Syphilis (twenty-nine cases). U. M. M. 1900. xiii. 634.—Tucker and Huger: The Value of the Justus Test. P. M. J. 10 May, 1902.

141. Zappert: Ueber das Vorkommen der eosinoph. Zellen im menschl. Blute. Z. M. **23.** 227. 1893.

142. Peter: Über das Vorkommen der eosinoph. Zellen bei Syph. und Hautkrankh. D. Zt. **4.** 669. 1897.

143. Grigorescu u. Galasescu: Die Hämatol. der Pellagra. Spitalul. **1903.** 19-20, 21. Ref. F. h. **1.** 172. 1904.—Neusser: Hämatol. Mitteil. W. k. W. **5.** 41. 1892.—Gollasch and Lukasiewicz, cit. by Neusser.

144. Leredde: Contrib. à l'étude histol. du mycosis fongoide. A. D. S. **5.** 509. 1894.—Leredde et Lafitte: Sur un cas de mycosis fongoïde. Ibid. **9.** 69. 1898.—Allgeyer: Mycosis fungoides und Leucocytosis lymphatica. Arch. scienc. med. **25.** 235. 1901.—Bensaude, cit. by Sereni: Nr. 145.

145. Fabre: Sur le mycosis fongoide. G. m. P. **1884.** Nr. 5.—Lukasiewicz: Ueber das erste und zweite Stadium der Alibertoshen Dermatose (Mycosis fungoides). Ar. D. S. **37.** 141. 1896.—Wolters: Mycosis fungoides. Bib. m. Abt. D. II. Hft. I. 1899.—Sereni: Mycosis fungoides. D. Zt. **11.** 41. 1904. (Further Literature quoted.)

146. Becker: Hämatol. Untersuch. D. m. W. **26.** 558. 1900.—Antse: Des modif. morph. du sang dans la syphil. Soc. russ. de Syphilogr. **1.** 261. 1891. Ref. A. D. S. **2.** 237. 1891. 2nd. I. D. C. 723. **1892.** Ueber morphol. Veränderungen des Blutes bei Syph. und einigen Dermatosen.

147. Canon: Ueber eosinop. Zellen und Mastzellen im Blute Gesunder und Kranker. D. m. W. **18.** 206. 1892.—For Literature see Meyer: Die klin. Bedeut. der Eosinophilie. 1905.

148. Reckzeh: Das Verhalt. der weissen Blutkörperchen, besonders der eosinop. Zellen bei einigen Erkrankungen der Haut, des Blutes und Infektionskrankh. D. Ar. M. **77.** 316, 1903.

149. Leredde: Étude du sang chez psoriasis au point de vue des eosinophiles. A. D. S. **8.** 213. 1897.

150. Jadassohn: I. D. C. (Lond.). 1896. P. 69. Discussion; also A. D. S. **7.** 1108. 1896.

151. Leredde: La dermatose de Duhring. Ga. h. **1898.**—Sur une hématodermite d'origine toxique. A. D. S. **9.** 1016. 1898.—Note sur les caractères anat. de la malad. de Duhring. Ibid. **7.** 846. 1896.—Lesions de la peau et du sang dans la dermatite pustul. en foyers à progression excentrique. Ibid. **8.** 1138. 1897.—Leredde et Pautrier: Hémodiag. dans un cas de dermat. de Duhring fruste. Ibid. **3.** 527. 1902.—Leredde: Dermatose de Duhring. Ibid. **10.** 711. 1899. Sur le pemphigus foliace de Cazenave. Ibid. **10.** 601. 1899. Valeur nosologique de l'éosinop. et de l'élimination de cellules eosinop. par la peau. Ibid. **10.** 355. 1899. Histo-hämatol. Untersuch. eines Falles von Hallopeau. Dermatitis. Die Beziehungen dieser Krankheit zur Derm. herpetit. Duhring und zum Pemphig. veg. Mo. D. **27.** 381. 1898. Sur une hématodermite d'origine toxique. P. m. **1898.** Mo. D. **29.** 136. 1899.

152. E. Leredde et Perrin: Anat. path. de l'herpes gestationis et de la dermatite herpetif. Ann. de derm. et de syph. **6.** 222. 1895.

153. Brocq: Ibid. **10.** 250. 1899. Discussion.—Darier: Dermatite herpetiforme. Ibid. **7.** 842. 1896.—M. Truffi: Intorno alla presenza di globuli bianchi a granulazione eosinofile in alcune mal cutane. Giorn. ital. della mal ven e della pelle. **33.** 757. 1898.—Wende and Pease: A Case of Dermatitis Herpetiformis illustrating an Unusual Pustular Variety of the Disease. Journ. of Cut. and Genito-urinary Diseases. **19.** 171. 1901.—Megnet et Pehu: De la dermatite

herpetiforme de Duhring-Brocq chez l'enfant. Annal. de derm. et de syph. **4.** 893. 1903.

154. Gaucher et Claude : Reflexion à propos d'un cas de derm. herpetiforme sur la nature de cette affection. Ibid. **7.** 1058. 1896.—Gaucher, Barbe et Claude : Dermatite herpetiforme (Étude micr. et chim.). Ibid. **6.** 567. 1895. —H. Hallopeau : Sur un cas de derm. herpetiforme sans éosinophilie. Ibid. **10.** 247. 1899.—J. Jaddassohn : III. Intern. Kongr. für Dermatologie und Syphilis. London. 4-8 Aug., 1896. Ibid. **7.** 1108. 1896.—Kaposi : Ueber den gegenwärtigen Stand der Lehre vom Pemphigus. Verhandl. des V. Kongr. d. Dermat. Ges. **5.** 13. 1896.

155. Bettmann : Ueber das Verhalten der eosinophilen Zellen in Hautblasen. Münch. med. W. **45.** 1229. 1898.—Gaucher et Bensaude : Sur un cas de lèpre avec granulomes lepreux miliaires généralisés, lésions de la muqueuse nasopharyngienne et de l'oreille moyenne et poussée lepreuse aignë erysipelatoide. Annales de derm. et de syph. **7.** 204. 1896.

156. Ehrlich : Die Anämie, in Nothnagel's Handb. d. spez. Path. u. Ther.

157. Hölscher : Ueber die Beziehungen zwischen Psoriasis und Asthma. Inaug. Diss. Kiel. 1893.—v. Noorden : Beiträge zur Pathologie des Asthma bronch. Zeitschr. f. klin. Med. **20.** 98. 1892.

158. Leredde : Étude sur le pemphigus foliace de Cazenave. Ann. de derm. et de syph. **10.** 601. 1899.—Leredde : Lésions sanguines dans l'urticaire. Ibid. **10.** 403. 1899.

159. Tschlenow : Die Veränderungen der Alkaleszenz des Blutes bei einigen Hautkrankheiten. Venerolog.-Dermatol. Ges. zu Moskau, and Wratsch. 248. 1898. Ref. Mo. D. **26.** 310. 1898, also Ann. de derm. et syph. **10.** 194. 1899.

160. Dacco : Ricerche ematologiche in alcune dermatosi. Eczema, psoriasi, dermatide efoliativa dermatosi a tipo bolloso. Lichen ruber planus, Prurigine d'Hebra, Acne volgare, Lupus volgare, Sarcoma di Kaposi. Giorn. ital. delle mal. ven. e della pelle. **38.** 405. 1903.

161. Jolles u. Oppenheimer : Ueber den Eiweissgehalt des Blutes Syphilitischer. Zt. Heilk. **24.** 1903.—Quinquaud : Des variations de la toxicité du serum sanguin dans les affections cutanées. Société de derm. Mai, 1893. Ann. de derm. et de syph. **4.** 619. 1893.

162. Dietrichs : Ueber die Ursachen der Erscheinungen nach ausgedehnten Verbrennungen des tierischen Organismus und ihre Behandlung. Russ. Arch. f. Chir. **1903.** Ref. Ctb. Chir. **31.** 95. 1904.

163. Kreibich : Ueber einige serodiagnostiche Versuche. Wien. kl. W. **15.** 699. 1902.

164. Hamburger u. Moro : Ueber die biol. nachweisbaren Veränderungen des menschlichen Blutes nach der Seruminjektion. Wien. klin. W. **16.** 445. 1903.

165. Rostoski : Verhandlungen der physikal.-mediz. Gesellsch. zu Würzburg. **35.**—Oppenheimer u. Michaelis : Mitteilungen über Eiweisspräzipitine. Arch. f. Anat. u. Phys. Physiol. Abt. Suppl. **1902.** 436.

166. Francioni : La Malattia da Siero. S. **1904.** 767.—Marfan et Le Ploy : La pathogénie des accidents sérotherap. Bu. H. Séance de mars 24 et de mai 19. —Pirquet u. Schick : Die Serumkrankheit. 1905.

167. Hayem : Du purpura. P. m. **1895.** 223.

168. Bensaude : Absence du rétraction du caillot sanguin et de transsudation du serum dans les diverses variétés du purp. hæmorrh. Soc. méd. des hôp. de Paris. A. D. S. **8.** 788. 1897.

169. Sicard : Caractère relatif au serum sanguin dans certaines variétés de purp. hæmorrh. C. r. S. B. 1. 7. 1899. Ibid. **10.** 1000. 1899.

170. Apert : Le purpura, sa pathogenie et celle de ses diverses variétés cliniques. Thèse de Paris. 18. 2. 1897.

171. Allacia : Recher. hæmatol. sur la purpura. R. c. P. **10.** 1903. Ref. F. h. **1.** 33. 1904.

172. Spietschka : Ueber einen Blutbefund bei Purp. hæmorrh. Ar. D. S. **23.** 265. 1891.

173. Lenoble : Les purpuras et leurs modalités cliniques d'après leur formale sanguin. A. D. S. **3.** 1097. 1902.

174. Riehl : Ueber Leucaemia cutis. I. D. C. P. 156. 1892.

175. Bisiadecki : Leukäm. Tumoren der Haut und des Darmes. W. J. **1876.**

—Hochsinger u. Schiff: Ueber Leucaemia cutis. Ar. D. S. **19.** 779. 1887.—Pinkus: Ueber die Hautveränderungen bei lymphat. Leukämie und bei Pseudoleukämie. Ibid. **50.** 37. 1899.—Nekam: Ueber die Leukämie. Erkrankung der Haut. 1899.—Jarisch: Hautkrankheiten, in Nothnagel's Handb. f. Pathologie. 1900.

176. Wagner: Prurigo bei lymphat. Anämie. D. Ar. M. **38.** 199. 1886.—Joseph: Pseudoleucaemia cutis. D. m. W. 15. 946. 1889.

177. Arning: Ein Fall von Pseudoleuk. mit multiplen Haut-, Schleimhaut- und Muskeltumoren. V. k. D. 1891. 2 and 3. 203. 1892.—Unna: Leukämie und Pseudoleukämie, Histopathol.—Fröhlich: Ein seltener Fall von Pseudoleukämie. W. m. W. **43.** 285. 1893.

178. Peter: Ueber Pityriasis rubra und die Beziehungen zwischen Hautkrankh. u. Pseudoleukämie. D. Zt. **1.** 345. 1894.

179. Wassermann: Lymphämie und Hauterkrankungen. D. Zt. **1.** 489. 1894.

180. Kaposi: Ueber eine neue Hautkrankh. Lymphodermia perniciosa. W. J. 129. **1885.**

181. Paltauf: Ueber lymphat. Neubild. der Haut. I. D. C. Wien. **1892.** 114.

182. Buschke: Ueber Prurigo lymphat. D. m. W. **28.** 837. 1902.—Funk: Ueber chlorot. Dermatosen. Mo. D. **28.** 551. 1899.

183. Wright: On the Treatment of Hæmorr. and Urticarias which are assoc. with a Deficient Blood-coagulab. L. I. 153. 1896; also On the Assoc. of Serous Hæmorrhages with Condit. of Defective Blood-coagulab. L. II. 807; also The Exaltation and Reduction of Blood-coagulab. by Therap. Measures. L. II. 1096. 1905.

184. Glaserfeld: Welche Beziehungen bestehen zwischen Haut- und Nierenkrankh. Diss. München, 1904.—Lassar: Ueber Erkältung. Ar. p. A. **79.** 168. 1880.—Ueber den Zusammenhang von Hautresorp. und Albuminurie. Ibid. **77.** 157. 1879.—Ueber den Zusammenh. von Hautödem und Albuminurie. Ibid. **72.** 132. 1878.—Hübner: Ueber Albuminurie bei Skabies. Z. M. **55.** 549. 1904.

185. von Leyden: Ueber das erste Stadium des Morb. Brightii und die akute oder frische Nephritis. Z. M. **3.** 161. 1881.

186. Liveing: Saccharine Urine in Chronic Eczema. L. **59.** 411. 1881.—Bruhns: Mehrere Fälle von acuter Nephritis bei Ekzem. B. k. W. **32.** 606. 1895.—Bluhm: Zur Aetiol. des Morb. Brightii. D. Ar. M. **47.** 193. 1891.—Pechkranz: Albumin. und akute diffuse Nephritis im Verlaufe einiger Hautkrankh. (Skabies, Ekzem). W. m. W. **49.** 2369. 1899.

187. Salvioli, cit. by Bruhns: Contrib. alla pathol. nei Reni I Glomerulo nefrite consec. ad eczeme impetiginosa diffuse della pelle etc. Ar. S. M. Vol. III. Fasc. IV. Jb. L. M. **1879.**

188. Lecorché and Talamon, cit. by Cesarini (189).

189. Cesarini: Sulle dermatosi albumin. Gi. M. v. **36.** 77. 1901.

190. Perrin: De la dermatose de Duhring au cours de la grossesse. A. D. S. **6.** 936. 1895.—Vilenski: De l'insuffisance rénale dans la dermatite de Duhring. Thèse de Paris. **27.** II. 1895.

191. Müller: Ein Fall von Nephritis bei Impet. contag. Ja. K. **31.** 64. 1890.

192. Senator: Ueber physiol. und pathol. Albuminurie. D. m. W. **30.** 1833. 1904.—Rubens: Ein Fall von akutem umschr. Oedem mit orthorat. Albuminurie. Mü. m. W. **52.** 854. 1905.

193. Welander: Über Nierenaffektionen bei Syph. Ar. D. S. **37.** 91, 323. 1896.

194. Senator: Die Erkrankungen der Niere. 1902.

195. Karvonen: Die Nierensyph. D. Zt. **7.** 37. 1900.

196. Schwimmer: Ueber das Vorkom. der Albuminurie bei luetis. Affektionen. W. m. W. **42.** 1913. 1892.

197. Petersen: Albumin. bei Syph. 10 I. M. C. Berlin. **1890.** Sect. of Derm. and Syph. Mo. D. **11.** 282. 1890.

198. Descoust: De l'albumin. survenante dans le cours des accidents second. dans le syph. Thèse de Paris. **1878.**

199. Hoffmann and Salkowski: Ueber Nephritis syphil. acuta praecox mit enormer Albumin. B. k. W. **39.** 113, 166, 190. 1902.

200. Fürbringer: Ueber Albumin. durch Quecksilber und Syphilis. 4. K. i. M. (Wiesbaden) **1884.**—Welander: Ueber Albumin. und Zylindrurie durch Syph. Mo. D. **15.** 45. N. m. A. **23.** Nr. 29.

201. Ott: Ueber Nukleoalbumin. im menschl. Harn. Z. H. **16.** 177. 1895. —Balzer et Jacquinet: Manifest. rénales de l'infection blennorrhag. Se. M. **13.** 411. 1893.

202. Balzer et Souplet: L'étude de l'albumin. compliquante les phases aigues de la blennorrh. Mo. D. **1894** (1893); also A. D. S. **1892.** Mo. D. **15.** 146.

203. Goldberg: Ueber Albumin. bei Blennorrhoe. Mo. D. **23.** 405. 1896.

204. Merck: Dermatoses albuminuricae. Ar. D. S. **43.** 469. 1898.

205. Djoritch: Sueurs d'urée en gén. et dans la mal. de Bright en particulier. Thèse de Paris. **1895.**

206. von Noorden: Die Zuckerkrank. und ihre Behandl. 160. 1898.

207. Gross: Ueber Beziehungen einiger Dermatosen zum Gesamtorganismus. W. k. W. **12.** 211. 1899.—Nagelschmidt: Psoriasis und Glycosurie. Diss. Berl., 1900; also B. k. W. **37.** 31. 1900.—Strauss: Ueber neurogene und thyreogene Glykosurie. D. m. W. **23.** 275. 1897.—Grube: Ueber Psoriasis (Schuppenflechten) in Zusammenhang mit Gicht und Diab. B. k. W. **34.** 1134. 1897.

208. Pick: Psoriasis und Glykosurie. B. k. W. **39.** 50. 1902.

209. Kaposi: Hauterkrankungen bei Diabetikern. Dermatosis diab. W. m. W. **34.** 1. 1884.

210. Colombini: Pentosurie und Xanthoma diabet. Mo. D. **24.** 129. 1897.

211. Sibirski: Ueber die Hautveränderungen bei Typhus abdom. R. Z. D. I. **1901.** Mo. D. **32.** 403. 1901.

212. Anschütz: Ueber den Diab. mit Bronzefärbung der Haut, zugleich ein Beitrag zur Lehre von der allge. Hämochromatose und der Pankreasschrumpfung. D. Ar. M. **62.** 411. 1899.

213. Rabé: Pathogénie du diab. broncé. P. m. **1902.** Nr. 16.—Caramanos: Des cachexies pigment. et en particulier des cachexies pigment. diabét. et alcooliques. Thèse de Paris. 1897.—Murri: Ueber Bronzediab. W. k. R. **1901.** Nr. 20. —Hess u. Zurhelle: Klin. und path.-anat. Beitr. zum Bronzediab. Z. M. **57.** 344. 1905.—Hess: Marburger med. Ges. B. k. W. **41.** 1231. 1904.—Osler: Clinical Remarks on Hypertrophic Cirrhosis of the Liver with Bronzing of the Skin: Hemochromatosis. B. M. J. 1595. **1899.** Beattie: Hæmochromatosis. J. P. and B. 1903.

214. Richardière: Cirrhosis hepat. mit Melanodermie. U. m. Dec., 1895. Mo. D. **23.** 253. 1896.—Kreissl: Hämochromat. der Haut und Bauchorgane bei idiopath. Hautatrophie mit Erythrodermie. Ar. D. S. **72.** 227. 1904.

215. Gigot-Suard, cit. by Blaschko: Autointoxik. und Hautkrankh. B. K. **87.** 15. 1895.

216. Quinquaud: Les éruptions conséc. à l'ingestion de l'acide urique. Die Hautausschläge der Harnsäurediathèse. A. D. S. **1.** 121. 1890.

217. Lewin: 2nd V. K. D. 1892.

218. Tommasoli: L'origine alloxurique de l'eczema. A. D. S. **1.** 801. 1900; also Ueber autotox. Keratodermitenden. 1893.

219. Bazin: Leçons théoret. et clin. sur les affec. cutanées de nature arthritique et dartreuse. 344. 1868.—Hardy: Traité des mal. de la peau. 753. 1886.— Brocq: Traitm. des mal. de la peau. 149. 1890. Gaucher: Pathogénie et metastase de l'eczème particul. chez les enfants. I. M. C. Paris. 538. 1889; also Leçons sur les mal. de la peau. Tome II. 1898.

220. Schmidt: Ueber die Altersveränderungen der elast. Fasern in der Haut. Ar. p. A. **125.** 239. 1891.

221. Unna: Basophiles Kollagen, Kollastin und Kollacin. Mo. D. **19.** 465. 1894. Elastin und Elacin. Ibid. **19.** 397. 1894.

222. Krzystalomicz: Inwieweit vermögen alle bisher angegeb. spezif. Färbungen des Elastins auch Elacin zu färben. Mo. D. **30.** 265. 1900.—Unna: Die Histopathol. der Hautkrankh. Myxödem. 1007. 1894.

223. Dreysel u. Oppler: Beitr. zur Kenntnis des Eleidins in normaler und pathol. veränderter Haut. Ar. D. S. **30.** 63. 1895.—Ernst: Ueber Hyalin, insbesondere seine Beziehung zum Kolloid. Ar. p. A. **130.** 377. 1892. Ueber die Beziehungen des Keratohyalins zum Hyalin. Ibid. **130.** 279. 1892.

224. Bosellini: Dei glicogeno cutaneo nelle dermatosi. Gi. M. v. **37.** 566. 1902; also Beitr. zum Stud. des Glykogens in der Haut bei Hauterkrankungen. Ar. D. S. **61.** 195. 1902.

225. Unna: Histopathol. of the Skin. Trans. by Walker. Edinb. 1896.
226. Greciet: Contrib. à l'étude de la sécrétion sébacée. A. D. S. **4.** 1242. 1893.
227. Arnozan: De la repartition des sécrétions graisses normales à la surface de la peau. A. D. S. **3.** 1. 1892.
228. Linser: Ueber den Hauttalg beim Gesunden und bei einigen Hauterkrankungen. D. Ar. M. **80.** 201. 1904.
229. Knöpfelmacher: Über das Fett im Säuglingsalter und über das Fettsklerom. W. k. W. **10.** 228. 1897; also Ja. K. **45.** 177. 1897.—Knöpfelmacher u. Lehndorff: Das Hautfett im Säuglingsalter. Z. e. P. **2.**
230. Langer: Mo. C. **2.** 382.
231. Weber: Sklerodermie. K. S. 1878.—Jeanne: Sur une maladie peu connue, caractérisée par des concrét. phosph. sous cutanées. B. S. P. **1900.**—Morell et Lavallée: Goutte et arthrit. R. T. **1901.**—Riehl: Ein Fall von Verkalkung der Haut. Mü. m. W. 49. 164. **1902.**—von Tannenhain: Zur Kennt. des Pseudoxanthoma elasticum. W. k. W. **1901.**
232. Wildbolz: Ueber Bild. von phosphorsauren und kohlensauren Konkrementen in Haut und Unterhautgewebe. Ar. D. S. **70.** 435. 1904.—Lewandowsky: Ueber subkut. und periartik. Verkalkungen. Ar. p. A. **181.** 179. 1905.
233. Merck: Ein Fall von Phosphatidrosis. W. k. W. **16.** 1091. 1903.
234. Adamkiewicz: Die Ausscheidungswege des Jodkaliums beim Menschen.—Guttmann: Bromreaktion des Inhalts von Aknepusteln nach längerem Bromkaligebrauch. Ar. p. A. **74.** 1878.
235. Jarisch: Die Hautkrankh. in Nothnagel's Handb. der Path. u. Ther. **1900.** 127.
236. Herxheimer: Ueber Chlorakne. Mü. m. W. **46.** 278. 1899.
237. Lehmann: Ueber Chlorakne. Ar. D. S. **77.** 265. 1905.
238. Samuely: Ueber die aus Eiweiss hervorgehenden Melanine. Bc. P. P. **2.** 355. 1902.
239. Wolff: Zur Kenntnis der melanot. Pigmente. Bc. P. P. **5.** 476. 1904.
240. Linser: Ar. D. S. **80.** 2.
241. Selenew: D. Zt. 1905. 569. **12.**
242. Gans: B. k. W. 1905. Nr. 22. **42.** 685.
243. Engman: J. C. D. **24.** 216.
244. Brocq and Ayrignac: A. D. S. **7.** 5, p. 433.
245. Gaucher et Desmoulières: J. P. P. G. March, 1905. **7.** 316.
246. Linser: Ar. D. S. **80.** 251.
247. Garrod and Pope: L. 1906. **1.** 24.
248. Helstedt: Ar. k. C. **79.** 2.—Eijkman u. Hoogenhuyze: Ar. p. A. **183.** 377.—Pfeiffer: Ar. p. A. **180.** 367.
249. Rzetkowski: Medycyna (Warsawa). **31.** 85. 121.
250. Brandweiner: Mo. D. Nov., 1905. **40.** 11.—Radaeli: Ar. D. S. **80.** 323.
251. Cabral de Lima: Arch. de l'instit. Camara Pestana. **1.** 1.
252. Hauck: Ar. D. S. **78.** 45. 289.
253. Wright: P. R. **72.** 357; and **73.** 128.
254. Bushnell and Williams: B. J. D. **18.** 5.
255. Linser: Ar. D. S. **80.** May, 1906, p. 3.
256. Herringham: St. B. H. Rep. **38.** 117.
257. Sahli: Z. M. **56.** (1905.) 264.
258. Fenwick and Parkinson: M.-C. T. **89.** 183.
259. Grosz: Be. A. P. **39.** Hft. 3.
260. Dubreuilh: A. D. S. Aug. and Sept., 1905. **6.** 8 and 9.
261. Ramazzotti: Gi. M. v. 1905. **40.** 163.
262. Paramore: B. J. D. **18.** 7 and 8; pp. 239 and 274.—Little: B. J. D. **17.** 12, p. 447, and **18.** 1, p. 16.
263. Veich: Ar. D. S. **80.** 59. (May.)
264. Lubarsch: Ar. p. A. **183.** p. 188.
265. Gierke: Be. A. P. **37.** Hft. 3.
266. Justus: Ar. p. A. **176.** 1.
267. Rosenfeld: Z. M. 27. (1906.) 986.
268. Ricciardi: Gi. internaz. d. Scienze Med. 38. (1906.) 18. 817.

CHAPTER VI

CANCER[1]

By ADOLF SCHMIDT.

Translated by W. Cramer, Ph.D., D.Sc.

When the investigation of metabolism was introduced into the study of clinical medicine, the question arose as to the cause of the cachexia of cancer. F. Müller (1) maintained, on the basis of careful analyses of the nitrogenous metabolism observed on cancerous patients, that in the cachexia of cancer we have to deal with a toxogenous disintegration of protoplasm independent of nutrition. In other words, a specific toxic effect of cancerous tissue exists. Up to the present date the entire literature on metabolism in carcinomatous patients centres around this last statement. At first it was generally confirmed ; later, however, it became doubtful, because it was recognised that the greater part of the anomalies of metabolism in cancerous patients was due to the mechanical effects of the tumour, the disturbances depending on the site, or, on ulcerative, or infectious, processes of the cancerous tissue.

Whether all the peculiarities of the metabolism of cancer can be explained in this manner has not yet been decided. The vigorous cancer researches of the last few years have brought this question again into prominence, and the adherents of the theories of the infectious nature of cancer believe that the existence of at least some of the toxic effects has been proved. It is best, therefore, that we should first concern ourselves with a critical review of the literature dealing with this question. We shall constantly have to keep in mind whether a disturbance which is supposed to be characteristic occurs generally in all cancerous diseases, or whether the disturbance is only a peculiarity of the cancerous degeneration of special organs. It must be remembered that most observations have been made upon cancer of the stomach—a condition which is least suitable for general conclusions to be drawn from. The few existing observations on malignant new growths other than cancerous will also have to be considered. Lastly, comparisons will have to be made with the cachexia associated with other than cancerous conditions.

[1] The term " cancer " is used for " carcinoma " throughout.

I.—INFLUENCE OF CANCER UPON THE DIGESTIVE PROCESSES.

A.—GASTRIC DIGESTION.

1. Secretion.

(*a*) *The Absence of Free HCl.*

In 1879 Van der Velden (2) observed the absence of free HCl in cases of cancer of the stomach. Since then this statement has been confirmed by so many observers that to-day it is one of the most assured facts in the pathology of the diseases of the stomach.

There are, of course, exceptions to this rule. Free HCl is present in about 10 to 13 per cent. of all cases of carcinoma of the stomach [B. Wagner (3), A. Richter (4)]. These exceptions can be explained by conditions where cancer is superimposed upon an ulcer of the stomach [T. Rosenheim (5)], which, as is well known, is frequently accompanied by an increased production of HCl, or by the simultaneous existence of a nervous hypersecretion [A. Richter]. As a rule, however, even in these conditions, the free HCl of the gastric contents eventually disappears, provided that the disease is in an advanced state, the change sometimes occurring rather suddenly [Koch, H. Schneider (6)]. On the whole, the absence of free HCl is rightly supposed to be an early symptom of cancer of the stomach [F. Riegel (7)]. Besides the free (that is, excessive) HCl, the values for the loosely-combined HCl (that is, HCl combined with albuminates) are much reduced [A. Cahn and J. von Mehring (8), G. Honigmann and C. von Noorden (9), Martius and Lüttke (10)], so that a more or less considerable deficiency of HCl exists.

Although it is easy to observe these conditions, their interpretation presents certain difficulties. Until recently, the general idea was that there was a diminished secretion of HCl in a cancerous stomach. In support of this view, we might adduce the catarrh of the gastric mucous membrane which frequently accompanies, and is probably caused by, the development of cancer, and which leads to atrophy of the glands [T. Rosenheim (11), A. Hammerschlag (12)]. This catarrh, however, is not of such a general and early occurrence and does not spread over the gastric mucosa so rapidly as to explain the absence of the free acid in the earliest stages of the development of small circumscribed tumours. Nor does the reappearance of the free acid after the removal of the tumour which has been observed in a few cases agree well enough with this assumption [T. Rosenheim (13), Bourget (14)].

A subsidiary hypothesis was next advanced—namely, that the development of cancer in itself exerts in a specific way an unfavourable influence upon the acid secretion of the stomach. If this is the case, then this influence should be observed with cancerous organs other than the stomach. Indeed, conditions of the gastric secretion similar to those observed in cases of cancer of the stomach have been found fairly con-

stantly in cases of carcinoma of the œsophagus, and frequently enough in cases of carcinoma of other organs.

These facts, however, do not justify the assumption of a specific peculiarity of cancer, as has been done by Moore and his collaborators in postulating a diminution in hydrogen ions in the blood of cancerous patients. When these cases are more carefully analyzed, it is found that either the individuals on whom these observations were made were markedly cachectic, or that the site of the new growth was in the proximity of the stomach. Cachectic conditions, however, must be excluded in discussing this question, for we know that the secretion of HCl is impaired in many severe illnesses, especially in severe anæmia (*cf.* Blood and Intestines); while malignant new growths situated in the proximity of the stomach, especially if there is any ulceration, may exercise their local influence in the same manner as cancer of the stomach.[1]

These local influences cause not only anatomical changes of the mucous membrane in the neighbourhood of the tumour; there are also chemical changes in the gastric contents which result from the action of the products secreted by the new growths. That such a local chemical interaction existed was made probable years ago by Riegel's (20) interesting experiment, and has been proved recently by the exact investigations of Reissner, in which not only the free and loosely-bound HCl, but also the solid chlorides of the gastric contents, were taken into consideration. Reissner was able to show that in cancer of the stomach the total chlorine percentage of the gastric contents does not suffer a decrease in proportion to the diminished HCl values, as is the case in other gastric diseases accompanied by a diminished HCl production, but that it nearly always maintains its average value even until shortly before death. Since there was no increased supply of NaCl, this result means that, even though the stomach has secreted HCl in normal quantities, the larger part of it must have been acted upon at once by basic, non-albuminous bodies. Further investigation showed that these bodies are fixed alkalis contained in the tumour-juice which is being secreted from the surface of the new growth. Such a secretion can, of course, only take place when the tumour is ulcerating, or when there has been at least a loss of superficial epithelium. It is known that malignant new growths of the stomach and of the adjoining parts of the œsophagus ulcerate at an early stage. Reissner is further justified in saying that often a loss of substance has taken place on the surface of tumours, even when the naked-eye appearances are still normal. It is certain, at any rate, that an increase in the fixed chlorides of the gastric contents appears nearly

[1] The results of a very extensive series of observations on thirty-four cases of carcinoma and four cases of sarcoma of organs other than the stomach or its proximity, have been published recently by Moore and his collaborators (182). In practically all cases there was a marked diminution in the secretion of hydrochloric acid. Their results have been confirmed by Parker (183), who examined fourteen cases of malignant new growths. Both Moore and Parker examined the gastric contents of patients suffering from non-malignant affections, and agree in finding almost regularly a diminished secretion of hydrochloric acid in non-malignant cases. Parker has paid special attention to the general condition of the patients, and comes to the conclusion that neither psychical influence nor cachexia can account for the diminution in the hydrochloric acid secretion, but that the diet and life in a surgical ward may be the cause.

always together with the absence of free HCl [von Tabora (22), Clowes and Jeffcot (23)].

There are still further proofs that there is a production of tumour-juice at an early stage. Stähelin (24) introduced into the empty and well-cleansed stomach of his cancerous patients a definite quantity of HCl, and observed after a short interval that a considerable portion of it had been neutralized by an alkaline juice. Rosenberger (24) showed, with artificial digestive mixtures, that the addition of small quantities of fresh cancerous tissue caused a neutralization of HCl. It will be later shown that this effect is due to the production of basic digestive products possessing an avidity for HCl. Finally, H. Salomon (25) observed that the liquid obtained from washing the empty cancerous stomach, which had been carefully cleansed the previous evening, contained greater quantities of protein matter and an increased percentage of nitrogen as compared with the contents of the stomach in other diseases. This fact, confirmed by several investigators (26, 27, 28), is not only of theoretical, but also of practical interest, because it may serve as a means for the early diagnosis of cancer of the stomach.

If all these numerous investigations in the secretion of HCl are taken together, we must conclude that in cancer of the stomach and of the adjoining organs (œsophagus, duodenum with gall-bladder and pancreas) it is not in most cases a question of a diminished production of HCl, but only a question of a rapid neutralization of HCl brought about by the secreted tumour-juice. Still, it may be admitted that the development of a malignant new growth anywhere in the body—even sarcomata are associated with a deficiency of HCl [Moore (18), Pstrokonski (29)]—may also influence the gastric secretion. This is, however, not a specific effect, but it is a consequence of the diminished resistance of the tissues, which occurs together with general cachexia and advanced anæmia.

(*b*) *Ferments.*

By the development of a malignant new growth in the stomach, the ferments of the gastric juice are less affected than is the case with the hydrochloric acid. From the investigations of A. Hammerschlag (12), R. Schorlemmer (30), B. Oppler (31), and others, it can be concluded with certainty that the action of pepsin and rennet continues long after the free HCl has disappeared. This fact also lends support to the view that it is not the secretion of HCl that is affected. Where there is a distinct decrease of the pepsin secretion, it may be explained by an anatomical or functional injury of the mucous membrane. This view is in agreement with the fact that in cases of tumours of the fundus the secretion of rennet and of pepsin is always simultaneously decreased, whereas in cases of tumours of the pylorus the secretion of pepsin alone is diminished, the secretion of rennet (which arises exclusively from the glands of the fundus) remaining normal [K. Glässner (32)]. It is not known how the ferments behave in cases of cancer of organs other than the stomach.

Apart from the physiological action of the gastric ferments, yet another

action, peculiar to cancer only, takes place in the gastric contents in cases of carcinoma ventriculi.

Starting from the observation that, as a rule, a large HCl deficiency exists in the carcinomatous stomach, even when the acidity is high, Emerson (24), in F. Müller's laboratory, analyzed most carefully the protein substances of the gastric contents. The result showed that one hour after the intake of a test breakfast an average of about 50 per cent. of the dissolved albumin had been transformed beyond the form of albumoses in the stomach of a normal individual, while in a stomach affected with cancer 72·5 per cent. had undergone this change. In the normal stomach there were 16·9 per cent., in the cancerous stomach 27·6 per cent. of nitrogenous substances which could not be precipitated by phospho-tungstic acid. These results have been confirmed recently by Rosenberg (33). By means of artificial digestion experiments, Emerson was enabled to throw light on this fact. He compared the digestion in a pepsin HCl mixture, to which a piece of fresh cancerous tissue had been added, with the digestion in a control mixture which contained a piece of boiled cancerous tissue. He found that the digestion of the protein substances was more advanced in the mixture containing fresh cancerous tissue than in the control mixture. This indicates clearly that cancerous tissue contains a ferment the action of which is similar to the ferment which effects autolytic processes. It has not yet been decided whether this ferment is a specific ferment peculiar to cancerous tissue, or whether it belongs to the class of the autolytic ferments common to all tissues. Since cancerous tissue exhibits a marked tendency for autolysis and for decay, the latter hypothesis is the more probable.

2. Motility and Absorption.

Through the development of cancer, the motility of the stomach suffers to a lesser or greater degree; frequently this takes place even at an early stage. Especially in cases of carcinoma of the pylorus, which are the commonest causes of stenosis of the pylorus, is the motility of the stomach impaired.

In these cases the constriction is due mostly to purely mechanical causes; spasmodic conditions may appear in the early stages, but they are of lesser importance than in the case of ulcers or of hyperacidity. The effects of carcinomatous constriction of the pylorus are the same as those of stenosis of any other origin. They lead to stagnation and decomposition of the gastric contents on the one hand, and to inanition on the other hand, so that we may here refer to the chapter on Gastric Diseases.

Similar symptoms, though rarely as prominent, may appear either in cases of carcinoma of the duodenum or gall-bladder, or in carcinoma of the pancreas. Malignant new growths of the œsophagus and of the cardiac end of the stomach, if they lead to constriction, cause inanition, together with stagnation in the œsophagus, while the gastric digestion may remain relatively intact.

The development of cancer in the stomach-wall must not necessarily be

an obstacle to the motility of the stomach, but in these cases too a slight disturbance of the motility is often found [Boas, A. Hammerschlag (12)]. When there is a constant appearance of lactic acid in the gastric contents, while HCl is absent, a simultaneous impairment of the motility must always be thought of, and careful analysis, as a rule, confirms this suspicion (see below). Extensive infiltration of the stomach wall, with cancer, may lead to an insufficiency of the pyloric ring, and then the stomach may empty itself more rapidly instead of more slowly.

Cancer of organs other than the stomach and its proximity has, as far as it is known, no effect upon the movements of the stomach.

Disturbances of the absorption from the stomach, resulting from the development of cancer, may occur, but they are practically of no significance.

3. Processes of Decomposition.

Each one of the two conditions occurring in cancer—namely, the absence of free HCl and the diminished motility of the stomach—is by itself sufficient to cause decomposition processes to occur in the gastric contents. If the two factors are combined, these processes are even more readily incited. This statement, based on facts which are discussed in the chapter on Diseases of the Stomach, holds good in cases of cancer of the stomach. Especially when the development of a tumour in the region of the pylorus has made it more difficult for the stomach to empty its contents into the duodenum, the contents stagnate and undergo an extensive decomposition, where various processes (lactic acid-, butyric acid-, alcohol- and acetic acid-fermentation, and putrefaction of protein) may be combined. When the mechanism which is responsible for the passage of food from the stomach is less affected, as is the case in cancer of the wall of the stomach, or in the early stages of cancer of the pylorus, lactic acid fermentation is, as a rule, the only abnormality. This process occurs at such an early stage that it has been thought to be a specific symptom of the development of cancer in the stomach.

In order to test this supposition, it is, of course, necessary that the lactic acid contained in the food (all our bread contains traces of it) should be excluded. Boas (34) succeeded in doing this by substituting porridge made from Knorr's lactic-acid-free oatmeal for the test breakfast recommended by Ewald.

From the results of numerous examinations in various gastric diseases, he concluded that the appearance of lactic acid in the gastric contents in cases of cancer might be considered as a specific symptom. He found that the lactic acid may frequently be absent in other non-carcinomatous diseases, although stagnation of the contents and absence of free HCl may exist; while in cancer it appears at an early stage, when these two factors are not yet pronounced. Very few investigators have accepted this interpretation [Ekehorn (35), Hammerschlag (12)]. Hammerschlag believed that the factor peculiar to cancer was due to the relative deficiency in pepsin. The majority of authors, however, have refused to accept Boas's view [H. Strauss (36), De Jong (37), Buhre (38), B. Wagner (3), Chiaruttini (39), Seelig (40)]. In a later paper even Boas himself

arrived at the conclusion that the formation of lactic acid is caused by the same factors in cancer of the stomach as in cases of benign gastric diseases—that is to say, that the cause must exclusively be looked for in the combination of impaired motility and a deficiency of HCl. Only, inasmuch as these two factors appear in cancer at the very earliest stage, often even before they can be detected by our experimental methods, is lactic acid a symptom characteristic of cancer. This may, perhaps, be explained by the existence of crypts and niches on the surface of the tumour, where small fragments of the gastric contents may undergo a local stagnation at the beginning of the disease. According to Sick (181), the formation of lactic acid is aided considerably by the products of decay of the cancerous tissue.

B.—INFLUENCE OF CANCER ON INTESTINAL DIGESTION.

The question whether the development of cancer has any influence on intestinal digestion has never been closely and comprehensively studied, because a specific influence on the functions of the intestine, similar to that which had been believed to exist in the case of the gastric juice, had never been observed or asserted. On the contrary, any disturbance of the intestinal digestion due to cancer (we have to deal here only with cancer of the digestive organs themselves) may be traced back without any difficulty to local influences, physical or chemical. We may therefore confine ourselves to a brief discussion of the various conditions which result from cancer, and refer for a detailed study to the chapter on Diseases of the Stomach and Intestine, where these conditions will be discussed at length, without regard, however, to their special relation to cancer.

Clinical experience teaches that cancer of the stomach is not necessarily followed by any intestinal disturbances, not even when the characteristic changes of the gastric functions, such as a deficiency in HCl, a slight disturbance of the motility of the stomach, or, again, a formation of lactic acid, could be clearly demonstrated. This corresponds to the conditions seen in achylica gastrica and in atony, the effects of which on the metabolism are also frequently limited to the gastric digestion.

Secondary intestinal disturbances, however, may occur in cancer of the stomach even at an early stage. In the first place, we meet here with the so-called gastrogenous forms of diarrhœa. They are caused by the deficiency of HCl, and the consequent insufficient digestion of the connective tissue contained in the food. They are brought about by putrefactive and fermentative organisms migrating into and settling in the intestine.

Since no special attention has been paid to the appearance of these diarrhœas in cancer of the stomach, I shall illustrate them by an example:

G. M., workman, sixty years, suffered from severe diarrhœa for about six weeks without having any symptom of gastric disorder. He was badly nourished, his teeth were defective, and his vertebral column somewhat stiff. Thoracic organs healthy; abdomen, no resistance, not sensitive to pressure; urine normal. No flatulence, no vomiting, and no stomach trouble whatever. Siphonage of the gastric contents was repeatedly tried, but the test breakfast could not even partly be recovered. The stools were constantly liquid, undigested connective tissue

and fragments of muscle being present, but no mucus. Microscopically, there were no abnormal appearances, especially no long bacilli. Neither fermentation nor putrefaction was present. By the rectum nothing abnormal could be felt. The diarrhœa proved intractable. The patient became more and more emaciated. *Post-mortem* there was extensive ulcerated carcinoma of the cardiac end of the stomach, with small metastases in the liver. The whole of the intestine was absolutely normal.

Further, inanition, frequently accompanied by constipation, will naturally appear so soon as the disturbance of the motility, or the vomiting following upon cancer of the stomach, becomes more pronounced. Lastly, when the cancerous growth extends to the transverse colon, the intestinal passage may be obstructed, or when the tumour begins to break down, a gastro-colic fistula may be established, and lead to lienteric diarrhœa.

The development of cancer in the duodenum, in the gall-bladder, in the liver, or in the pancreas, is considered to be the cause of disorders of biliary or pancreatic secretion. The symptoms of these conditions are discussed in the chapter on Intestinal Diseases. An extensive carcinomatosis of the liver may cause coma carcinomatosum (see below, Parts III. and V.), just as carcinoma of the pancreas may account for the occurrence of diabetes (*cf.* Diabetes).

The function of the intestine may be affected in a great many ways by cancer of the intestine, the disturbances varying according to the site of the tumour, its mode of spreading, and the extent to which it is necrosed. The secretion of the intestine is not, as a rule, impaired to any considerable extent, except when whole areas of the intestinal mucous membrane are affected; it need, therefore, not be considered. The mechanical functions may show various grades of impairment, ranging from stenosis to complete occlusion, with their subsequent phenomena. Diarrhœa occurs specially in the case of necrosed tumours; it may be due to stimulation of the motor nerves of the intestine, but more frequently it is the consequence of extensive processes of decomposition.

The absorption is, of course, always affected whenever there is diarrhœa, or when the secretion of the gall-bladder and of the pancreas is impaired. Cancer of the stomach or of more remote organs (œsophagus, uterus, penis) does not necessarily interfere with the absorption, as the careful metabolism experiments of F. Müller (1) and G. Klemperer (2) have shown. The excretory activity of the intestine may be disturbed by malignant new growths in the colon or in the rectum. In such a case the rectum secretes frequently an abundance of mucus, pus, and blood.

Lastly, the putrefactive processes in the intestinal canal have to be discussed. They may be increased in the case of any malignant new growth of the intestinal canal, either because important secretions are wanting, or because the motility is diminished, or, lastly—and this is certainly the commonest cause—because ulcerative processes take place on the surface of the tumour. In this last condition the effect is brought about in a twofold way. Substances are secreted which are easily decomposed, while at the same time a good nutrient medium is offered to putrefactive organisms. We should therefore not be surprised to meet with symptoms of an increased putrefaction of the intestines in the great majority of cases of intestinal carcinoma. Since the

putrefactive processes in the intestine have up to now been studied only in the products of putrefaction, which reappear in the urine as phenol, indican, etc., without reference to the substances contained in the fæces, these conditions will be discussed in the section on Urine. The question whether malignant new growths of organs other than those of the digestive tract affect the putrefactive processes in the intestine will also be dealt with in the same place.

II.—EFFECT OF THE DEVELOPMENT OF CANCER UPON THE BLOOD.

During the development of cancer the blood frequently undergoes changes which manifest themselves clinically as a more or less severe anæmia. Here again it is especially cancer of the stomach that is associated with anæmia, while cancer of the uterus and other internal organs comes next in order. Though the anæmia is by no means a constant symptom of the growth of cancer, some investigators insist on its being a specific effect of the hypothetical cancer toxin.

A.—INFLUENCE OF CANCER ON THE BLOOD.

1. The Red Blood-Corpuscles.

It has long been known that the red blood-corpuscles are diminished in cancer (43 to 56). All observers agree that in the earliest stages the decrease is small and hardly noticeable, while exceedingly low values may be found in more advanced cases. There is, however, not a strict parallelism between the degree of anæmia and the degree of cachexia, or—since the conception of cachexia includes a certain amount of anæmia—the emaciation of the patient. A considerable diminution of the red blood-corpuscles occurs sometimes in the earliest stages of carcinoma, especially of cancer of the stomach [Laker (57)], when the internal organs have undergone but slight changes. It has been suggested to make use of this symptom in a differential diagnosis from gastric ulcer. But the results of observation vary too much. Besides, small hæmorrhages may diminish the number of erythrocytes even in very early stages of gastric ulcer. According to Henry (54), 1,500,000 per c.mm. is a minimal value, any further decrease suggesting the diagnosis of pernicious anæmia. But, as von Limbeck, E. Grawitz (61), and Lubarsch (58) have observed values below 1,000,000 per c.mm., no definite law can be established. As a rule the figures range above 2,000,000.

There are, however, cases of malignant new growths where the opposite condition appears, because the site of the tumour produces an impairment of absorption (œsophagus, fundus, pylorus). This may lead, not only to a lack of water in the tissue, but also inspissation of the blood, so that it flows "like tar" from the blood vessels. In these conditions the number of blood-corpuscles per c.c. is increased, although the total number may still, of course, be diminished.

In the anæmia of cancer, the form of the red corpuscles may vary, just as in secondary anæmia. Poikilocytosis, micro- and macrocytes [according to Malassez, Osterspey, Strauer, and others] may be found. Normoblasts and even megaloblasts have been observed [Grawitz, Rencki]. Megaloblasts, however, are rare, and normoblasts occur less frequently than in other forms of anæmia. In any case, the view maintained by Jez that they are more numerous, especially in the early stages, does not agree with the facts. Nor does, in the anæmia of cancer, the bone-marrow constantly show signs of an increased function. Constant relations between the degree of anæmia and the appearance of the bone-marrow cannot be established in cancer [Schur and Loewy (63)]. The investigations made by Lang (64) have shown that the resistance of red blood-corpuscles to a hypotonic NaCl solution is increased in cancer, showing in this respect the same behaviour as during infective processes and icterus.

2. Specific Gravity and Percentage of Hæmoglobin in Blood.

The specific gravity of blood is diminished in cancer. The normal specific gravity ranges from 1·0591 for men to 1·0562 for women. In this respect the observations of all the authors agree (64 to 69). Grawitz found values of 1·046 and 1·040, and Boas 1·0275 and 1·0272. The cause for this phenomenon is to be found in the diminished percentage of hæmoglobin, which in turn depends upon the reduced number of red blood-corpuscles. At all events, most investigators (see above, under 1) find an almost parallel decrease of both factors. Häberlin (70) and Engelsen (71) stand alone in maintaining that the diminution of the percentage of hæmoglobin is greater than that of the number of erythrocytes. However, the results of more recent investigations [Rencki, Krokiewicz] refute their statements.

The diminished percentage of hæmoglobin, as well as the decrease in red blood-corpuscles, is independent of the cachexia—that is, of the emaciation and loss of strength [Laker (57)]. In cancer, 60 per cent. of hæmoglobin is found on an average, the lowest value which has been observed being 10 per cent. [Häbelin (70), Eichhorst (72)].

3. Percentage of Nitrogen and Protein Substances.

A diminution of the nitrogen percentage of the blood and of the protein percentage calculated from it has been observed by von Jaksch (73). His figures are as low as 8·46 grammes protein. According to H. Wendelstadt and L. Bleibtreu (74), the nitrogen percentage of the serum also is often decreased in cancer. In one case of cancer of the stomach 100 grammes of blood contained 0·79 gramme nitrogen, instead of 2 to 2·5 grammes, as is found normally.

4. Dry Residue.

In the anæmia of cancer, the dry residue of the blood is decreased [Stintzing and Gumprecht (75)]. This holds good not only for the total

blood, but also for the serum [E. Grawitz (68)]. One is justified, therefore, in speaking of a dilution or a watery condition of the blood.

Considered together, the changes of the blood in cancer form a group of symptoms which may also be met with in the most varied forms of secondary anæmia. The anæmia of cancer is a constituent part of the cachexia of cancer, although, as we have seen, it by no means keeps pace always with the emaciation and with the loss of strength. How it originates is a question which it is difficult to answer, and is as yet an unsolved problem.

By drawing an analogy with myoma of the uterus, gastric ulcer, etc., we might think at first of chronic losses of blood, and many facts lend support to such an inference. There is, for instance, the marked frequency with which the anæmia of cancer is met with in malignant new growths of the uterus and of the intestinal tract—that is, in tumours which either lead to manifest hæmorrhages, or, where the occurrence of less extensive and less apparent, hæmorrhages can easily be demonstrated (gastric and intestinal cancer). Boas and Kochmann (76) even consider the absence of these small hæmorrhages as exceptional, a view which is refuted by B. Wagner (3) and others. It is certainly a remarkable fact that in gastric ulcer, where, as a rule, more or less extensive hæmorrhages occur regularly, severe anæmia is met with less frequently than in cancer. This might be due to the regenerative powers of the blood in gastric ulcer being greater than in cancer, where the general cachexia and the frequent formation of metastases in the osseous system interfere with the transformation of yellow into red marrow.

A second possible explanation of the origin of the anæmia of cancer may be sought for in the absorption of hæmolytic products from the cancerous surface. This view is borne out by the fact that anæmia is associated especially with the later stages of cancer, when, in the majority of cases, —at any rate, in cancer of the intestinal tract—ulcerations on the surface are already existing. Besides, certain forms of anæmia in septic conditions offer many points for comparison. There are, however, certain facts which are not in accordance with this idea. The anæmia of cancer is often not accompanied by fever, and especially in cancer of the stomach it may occasionally appear at a stage when the tumour is still circumscribed, and certainly not ulcerating, and when it has not yet brought about any functional disturbances. Such cases have been described by Grawitz and others, and have repeatedly come under my own observation.

Lastly, it is possible to ascribe the anæmia of cancer, as do the majority of authors, to specific toxic substances secreted by the cancerous tissue and entering into the blood-stream. This hypothesis takes its origin from the view expressed by F. Müller (1) that the cachexia of cancer is a toxogenous metabolism of protoplasm, a view which we shall have to discuss in greater detail later on. Although the hypothesis of the specific hæmolysis of cancer is one which at first sight appears to be very plausible, its experimental foundations are at present still very insufficient. Grawitz (77) injected intravenously the extract of fresh cancerous tissue into rabbits, and observed it to have the effect of " thinning " the blood. In some cases, Micheli and Donati (78), as well as Kull-

mann (79), detected hæmolytic properties in extracts of carcinomatous tissue. Bard (80) observed the same in hæmorrhagic transudates in cancer. While these results are very interesting, they do not suffice to settle the question, for the hæmolytic substances may just as well have been absorbed by the ulcerating surface. We are not justified in drawing far-reaching conclusions with regard to the "specificity" of the condition, for experience has taught us that the anæmia of cancer does not present any features which would distinguish it from other secondary anæmias, and that all attempts to use any one symptom for a differential diagnosis have up to now failed. As we shall return to this question at the end of this chapter, we shall not proceed here any further with the discussion of the anæmia of cancer.

B.—THE EFFECT OF THE DEVELOPMENT OF CANCER UPON THE LEUCOCYTES.

In contrast with the red blood-corpuscles, the number of leucocytes is generally increased in cancer. This fact has been known for a long time, and has been confirmed, especially in recent years, by numerous investigators (81 to 89, 46 to 55). The figures which have been obtained are, on the whole, however, not very remarkable, for in only a few cases do they exceed 10,000. Nor is leucocytosis in any way a constant accompaniment of the growth of cancer. Just as the decrease of red corpuscles, leucocytosis is not strictly proportional to the degree of cachexia, even though it increases, generally speaking, with the growth of cachexia. In connection with this, it is perhaps of interest to note that one frequently fails to find a leucocytosis in cases of a carcinomatous stenosis of the œsophagus [Escherich, Rieder (90)].

The origin of leucocytosis was considered by Virchow to be due to the irritation of the glands by metastatic deposits, a view which has been accepted by Ehrlich and Einhorn (91). The complete destruction of the glands by cancer is supposed to reduce the leucocytosis [Einhorn, von Noorden (60)]. Escherich and Rieder, as well as Grawitz (61), who bases his view on his experiments on rabbits, attribute the leucocytosis to an increased afflux of lymph to the blood.

In any case, we should expect an increase of the lymphocytes to be the essential feature of the leucocytosis. There are, however, a few observations on record where the increase was due to polynuclear leucocytes [Strauss and Rohnstein, Rieder (90)]. Besides, all investigators, even Grawitz, admit that the relative numerical proportion of the various forms of leucocytes is not altered in a uniform manner [*cf.* Donati (101)]. There are even instances in which the eosinophilous cells are especially numerous [Reinbach (92), Feldbausch (93)]. A satisfactory explanation of the leucocytosis of cancer is still wanting. Another factor has yet to be taken into account—namely, that in the late stages of tumour growth certain infective organisms enter the tissues from the ulcerating surface, and produce a secondary sepsis [Rencki].

The absence of the digestion leucocytosis was asserted by Schneyer (94)

to be a special peculiarity of gastric carcinoma which might be made use of for diagnostic purposes. Normally, the digestion leucocytosis takes place between the third and fourth hour after a meal. The increase of leucocytes, which amounts to about 3,500, is supposed to be due to the digestion of the protein substances. Schneyer's work led to a great number of similar observations, but only few authors have confirmed his statements, and even then only with essential limitations [Hartung (64), Jez (62)]. The greater majority conclude that the digestion leucocytosis is not invariably absent in cancer of the stomach (95 to 101). On the other hand, the absence of digestion leucocytosis is of such frequent occurrence in other gastric diseases (such as catarrh and gastric ulcer), and in cachexia due to other causes, that it is by no means characteristic only of cancer of the stomach. Under these circumstances, it is hardly necessary to consider more closely the various views as to the cause of this phenomenon. All of these are based upon the idea that there is an insufficient absorption of protein substances.[1]

C.—OTHER CHANGES IN THE BLOOD IN CANCER.

1. Alkalinity.

The decrease in the alkalinity of the blood which obtains in other forms of severe anæmia occurs also in the anæmia of cancer, especially in its advanced stages. It may be inferred from this fact, which has been ascertained by different methods and by a great number of observers (102 to 107), that under these conditions abnormal acids are circulating in the blood. According to von Noorden (60), inorganic acids, such as sulphuric and phosphoric acids, which are liberated by the increased katabolism of the tissue protein, play the most important part. This view implies a parallelism between the decrease of alkalinity and the destruction of the body protein—*i.e.*, the stage of cachexia—a relation which has not yet been established. According to H. Strauss, who used the most reliable method—namely, Loewy's method of titrating laked blood—the decrease in alkalinity is by no means constantly associated with the development of cancer, both subnormal and normal values, and even supernormal, being obtained. It is therefore more plausible to ascribe the decrease of alkalinity to the presence of acetic and β-oxybutyric acid, and to assume here an acid intoxication, such as takes place in inanition—a condition so frequently associated with the development of cancer. Further investigations, however, are required to settle this question.[2]

[1] In a recently published paper Baradulin (187) states that the digestion leucocytosis is almost always absent in cancer of the stomach. This paper deals also with other changes in the blood.

[2] By a new method of titration, Moore and Wilson (185) have determined the alkalinity of the serum in a number of cases of malignant and non-malignant disease. They find a slight but distinct increase in the alkalinity of the serum of malignant cases. According to Moore, this slight increase in the alkalinity of the blood is the cause of malignant disease. It is also responsible for the diminished secretion of hydrochloric acid in the gastric contents (*cf.* p. 799).

2. Chlorine—Phosphorus.

The chlorine and phosphorus percentage is another point in which the anæmia of cancer resembles other forms of anæmia. By extensive analyses, W. von Moraczewski (108) has shown that a retention of these two elements takes place. This is especially the case with chlorine, which in cancer accumulates at a much higher hæmoglobin percentage than, for example, in chlorosis.

3. Percentage of Sugar.

E. Freund (109) found regularly in the blood of cancerous patients an increased percentage of sugar up to 0·33 per cent. This statement was confirmed by Trinkler, who investigated 120 cases. It appears, therefore, that some importance must be attached to this fact, and that one cannot agree with Matrai (111), who does not consider it to be a characteristic feature of cancer, since the percentage of sugar in other severe forms of anæmia may also be occasionally increased. However that may be, the bare fact alone does not justify any further conclusions.

4. The Amylolytic Power of the Blood.

This is said by Achard and Clare (112) to be diminished in the cachexia of cancer.

5. Osmotic Pressure.

Israel (113) and Engelmann state that in cancer the osmotic pressure of the blood-serum, as measured by the depression of the freezing-point, is higher than normal. Engel (115) has recently contradicted this statement. He never observed the freezing-point to be below the normal, if he excluded the fallacies which may be introduced by the simultaneous existence of an arterio-sclerosis, an acetonæmia, an incompetency of the kidney, or an insufficient oxygenation of cyanotic blood.

6. Toxicity of the Blood.

G. Klemperer (179) observed in dogs an increased protein katabolism after intravenous injection of the blood of cancerous patients. This single observation has, however, not yet been confirmed.

7. Hæmolytic Power.

Ascoli and Kreibisch have observed an increase in the hæmolytic power of blood-serum of cancerous patients. These observations refer only to the presence of isolysins. Should these results be confirmed by others, it is possible only to conclude that the substances which have been

found in the extracts of malignant new growths are absorbed into the circulation [Micheli and Donati (78), Kullmann (79)].

If we review the observations grouped together in the Sections B and C, we must conclude that they give just as little evidence for the presence of a specific cancer toxin in the blood as the facts which were discussed in Section A. All the various statements, disconnected as they often are, which refer to the changes of the leucocytes and to the chemical composition of the blood, have in a similar way been advanced in other severe anæmias, especially in pernicious anæmia. Their explanation may be found in the combination of two factors—the destruction of the blood, and its insufficient renewal. These are symptoms which frequently, though not regularly, accompany the cachexia of cancer. Although it may appear plausible to ascribe the destruction of blood to the action of toxic substances, it cannot be urged too strongly that a positive proof of the existence of the supposed toxic agent is up to the present day still lacking. Even the increase in the hæmolytic power is no conclusive evidence, although great stress has been laid upon these observations; for such a condition has been observed also in various other pathological processes—*e.g.*, in pneumonia, etc. But even if the existence of a cancer toxin in the blood had been proved conclusively, it would not follow that the toxin is endogenous, that it originates in the cancer tissue itself. It may just as likely have penetrated into the tumour from the exterior through the frequently ulcerated surface.

III.—INFLUENCE OF CANCER UPON THE NUTRITION AND THE DECOMPOSITION OF PROTEIN.

In the foregoing sections we have repeatedly mentioned the cachexia of cancerous patients. This is a peculiar group of symptoms which, though not occurring exclusively in cancer, is so closely associated with the advanced stages of the disease that it is quite characteristic of it. Besides the anæmia which we have just discussed, the cachexia of cancer includes emaciation and a decline of physical strength. With these main symptoms there also occur dryness of the skin, falling-out of hair, loss of appetite, insomnia, and psychical depression.

The emaciation and the loss of physical strength proceed together in the cachexia of cancer. They may advance more rapidly in some cases than in others, but they invariably appear in all cancerous patients, and it is unnecessary to discuss the degree to which they may develop. A very early loss of the body-weight occurs, as a rule, in cancer of the digestive organs. According to the view of von Noorden, which is, however, hardly meant to be taken as a universal rule, the muscular apparatus of cancerous patients is most affected. He holds that, comparatively often, one meets with carcinomatous patients who, with good fat reserves, are yet pining away with loss of muscular power. In any case, it is an established fact that weakness is complained of at an early stage, when the nutritive condition may still be pronounced as being fairly good.

A.—INANITION.

The causes of the emaciation of cancerous patients are not uniform. Various factors are at work which have to be analyzed in order to arrive at a satisfactory explanation. Firstly, we have to consider the insufficient nutrition or inanition. This is either due to a loss of appetite, or it is caused by mechanical obstacles which prevent the intake of food. The insufficient absorption of food brought about either by cancerous degeneration of important digestive glands, or by a secondary disease of the intestinal mucous membrane, must also be taken into account here. As a rule, several of these factors act simultaneously.

The loss of appetite appears, as clinical experience teaches, at an early stage, not only in cancer of the digestive organs, but also in all other forms of cancer. Von Noorden determined in three cases of cancer of the stomach, and in six cases of cancer of the uterus, the nutritive value of the daily food chosen by the patients themselves, and obtained the low figures of 300 to 1,200 calories pro die, or 18 to 28 calories per kilogramme of body-weight.

It seems a matter of course, therefore, that emaciation and the breaking down of fats and of muscular substance should occur. By stimulating the appetite by means of successful psychical therapeutics and a careful selection of food, the loss of weight can be checked in some cases; but it is difficult to keep up a plentiful supply of food permanently, because the patients soon refuse the food.

The supply of food is, of course, still smaller in cases where mechanical impediments, such as constriction of the œsophagus, of the cardiac end or of the plyoric end of the stomach, are present. Such conditions may lead to complete inanition. Since we shall have to return to this point later on, we shall only mention here that, according to observations made on Cetti, Breithaupt, and others who submitted themselves to an acute state of starvation, a man loses during the first ten days about 10 to 11 grammes, a woman only from about 4 to 6 grammes. In cases of chronic malnutrition, when, on account of a gradually decreased food-supply, the body is slowly wasting, the organism can maintain its equilibrium with far smaller nitrogen quantities. For females 3 to 4 grammes nitrogen have been observed to be sufficient [Fr. Müller (1), von Noorden (119)]. It is unnecessary here to dwell on the disturbances of the absorption which may be brought about either by the cancerous degeneration of the digestive glands, such as the liver and pancreas, or by the closing of their excretory ducts by the proliferation of malignant new growths. These conditions will be dealt with in the chapter on Intestinal Diseases. We only wish to call attention to the fact once more that diarrhœa frequently appears, not only in cancer of the intestine, but also in cancer of the stomach. The nutrition, already impaired, will then, of course, be still further affected [Fr. Müller and others].

B.—PATHOLOGICAL DISINTEGRATION OF THE TISSUE PROTEIN.

Malnutrition may not be the only cause of the loss of body-weight and of the loss of strength in the cachexia of cancer. There is yet another factor which is, however, not easily demonstrated, and has therefore given rise to much discussion—namely, a pathologically increased disintegration of protein. After a great many investigators had unsuccessfully attacked this problem, it was solved—at least, to a certain extent—by the important investigations of F. Müller in 1889. By a careful analysis of the metabolism of various cancerous patients not suffering simultaneously from fever or from œdema, he found that the nitrogen losses of certain patients suffering from gastric cancer exceeded considerably the amount that could be explained as being due to the existent inanition. The abnormally increased disintegration of protein was even more conspicuous in a patient suffering from carcinoma of the penis, whose intake of food was normal. In this instance Müller found it impossible to balance the increase in the protein katabolism by an increased food-supply. Not even with the aid of a daily supply of 21 grammes of nitrogen and a caloric food value of 3,064 calories could a nitrogenous equilibrium be established; the output still exceeded the intake. Müller investigated altogether seven cases of cancer of different organs. In two—a carcinoma of the pancreas and a carcinoma of the mamma—the protein losses were not greater than could be expected from the state of inanition. Healthy persons in similarly poor nutritive conditions would have excreted about the same amount, so that these two cases did not give any evidence of a specific effect of cancer on the metabolism. In four cases of cancer of the stomach, however, the findings were of a different nature. The intake of food was reduced to such a considerable extent that the patients, all of whom were women, were in a state almost approaching starvation; but the nitrogen excretion exceeded that of healthy individuals under the same nutritive conditions, and amounted to 8·3 to 12 grammes nitrogen per diem. The seventh and last case was that of the carcinoma of the penis mentioned above.

Müller's results are of special interest, and I have given them in detail because they show that the pathological protein katabolism cannot be demonstrated in all cases of cancer. This has been confirmed by the work of all observers who have investigated this problem after Müller (120 to 127). Although few of them have been as careful in the selection of their material and in the accuracy of their methods, they have nevertheless shown that cancer may be associated with a completely normal protein metabolism. As more and more cases were investigated, it was found that the number of cases with a normal protein metabolism exceeded those with an increased protein katabolism. In fact, cases were observed in which even a nitrogen retention occurred [Schöpp (144), von Moraczewski]. It would be a mistake, however, to deny, on the basis of these observations, the existence, or rather the occurrence, of an abnormal disintegration of protoplasm in cancer. Firstly, the retention of nitrogen

does not necessarily indicate a positive balance of protein. In the late stages of the disease, in spite of an increased protein katabolism, a retention of nitrogen is not at all rare, as Müller has already pointed out, simply because the excretory organs fail to perform their functions. Secondly, we should expect that, in the course of a chronic disease associated with the decomposition of the proteins of the body, there will be a period in which the disintegration may be temporarily arrested, or may even be over-compensated by improved nutritive conditions. In cases of inanition due to a stenosis by malignant new growths, such improvements are well known to occur when the tumour obstructing the passage has been removed, either by breaking down of tissue or by operation. Cases are not rare where a dilatation of the cancerous stricture of the œsophagus is followed by an increase in weight of 10 to 20 pounds within a few weeks.

Lastly, von Noorden has pointed out that under certain circumstances it is possible to mask the protoplasmic disintegration in cancerous patients. For the increased protein metabolism can be lowered, just as in fever, by giving a diet rich in carbohydrates. Altogether, the cancerous destruction of protein resembles the febrile protein katabolism in many respects. In both conditions the fat of the body is much less affected than the muscular substance; if the fat is used up, inanition is usually present too. F. Kraus (128) and N. Svenson (129) have shown that in cancer the oxygen consumption reaches the higher limit of the normal values, and may even somewhat exceed the normal limit. This increase in the oxidation is, however, not in proportion to the extent of the protein katabolism. The same holds good in the case of fever. In the following paragraph we shall meet with various disturbances of the metabolism which are common both to the cachexia of cancer and to fever.

If we try to explain the pathological disintegration of proteins in cancer, the analogies with the protein katabolism in fever suggest an interrelation with the infectious processes appearing so frequently in cancer, which take their origin from the ulcerated tumour surface. Such a view would identify the protein katabolism of cancer with that of fever. Indeed, if special attention is paid to the temperature, careful observation of many cases of cancer, especially those of cancer of the internal organs, reveals a rise in temperature [in about 40 per cent., according to Freudweiler (130)]. As this factor has not been considered in most of the cases which have been used for observation on the metabolism, they are open to serious objections. Only Müller's investigations stand this test, as they have been made exclusively upon patients without fever. We must therefore maintain that the protein katabolism of cancer may occur independently of a rise in temperature, although in some cases it will probably be accounted for by the fever.

A second factor which may lead to abnormal losses of protein may be looked for in the discharge of disintegrated tissue from the surface of ulcerated and putrefying tumours. Up to now sufficient importance has not been attached to this fact, but I am of opinion that its significance should not be underrated. H. Salomon (25) observed that in the earliest stages of cancer of the stomach, when the tumour was not yet to be felt, the washings of the empty stomach contained regularly about 0·01 gramme

of nitrogen, which was secreted by the tumour. How much greater must the daily loss of nitrogen be from large ulcerating tumour surfaces ! In all cases of cancer, where the metabolism had been investigated, even in those of Müller's, there existed tumours of the stomach which were either undoubtedly ulcerated, or were, at any rate, so large that they could easily be felt and were, therefore, likely to possess an ulcerating surface. In any case, this factor will always have to be considered before the assumption of a new and far-reaching hypothesis can be justified.

The theory which I am referring to is the doctrine of a specific toxogenous disintegration of proteins. It has been advanced by F. Müller, and has been accepted by the majority of later writers [Klemperer, von Noorden, and others]. Objections have been raised by some authors [Braunstein (124), F. Blumenthal (131)], who argue from the steadily-increasing observations of a normal nitrogen metabolism in cancerous patients. If it is further mentioned that the reliability of those investigations which have hitherto been accepted as fundamental is called in question by the fallacies to which we have drawn attention, we must hesitate in accepting the theory without further evidence. Müller himself designates his view " as yet hypothetical." How very slowly and almost imperceptibly does the emaciation proceed in those cases where the growth is not in connection with the exterior, where ulcers, fever, and impairment of nutrition are absent ! Take, for instance, the condition where metastatic new growths aref ormed after the removal of the primary cancer of the breast or of the testicle, or the case of general carcinomata arising from the prostate. And how long can patients with cancer of the œsophagus and of the stomach maintain good nutritive conditions if, under exceptional circumstances, the appetite has not been affected, and no obstruction has taken place ! But even such patients eventually fall a prey to emaciation, and, excepting those cases where special circumstances hasten death, a cancerous patient rarely dies without showing the symptoms af cachexia. Although conclusive evidence for the presence of a specific toxic agent has not yet been adduced, the possibility of its existence must not be excluded. Our knowledge of this subject does not exceed our information on the anæmia of cancer, and we wish to emphasize here what we pointed out there—namely, that even if the existence of a toxic agent should have been established, it would still have to be proved that it is endogenous in origin, being formed within the tumour tissue itself. It may just as well have penetrated into it from without, through the excoriated epithelium.

IV.—THE INFLUENCE OF THE GROWTH OF CANCER UPON THE URINE.

In the course of the development of cancer, the composition of the urine undergoes many changes. These are either associated with disturbances of the metabolism already discussed, or they depend on other

less-known anomalies. None of these causes exercise a characteristic influence either on the amount, or on the specific weight, or on the reaction of the urine.

A.—THE VARIOUS NITROGENOUS CONSTITUENTS.

G. Töpfer (133) was the first to draw attention to the fact that in cancer the nitrogenous end-products of protein metabolism do not appear in the urine in the same proportions as in normal individuals. While in the normal urine the distribution of nitrogen was found to be 96 per cent. for urea, 1·8 per cent. for uric acid, 1·2 per cent. for NH_3, and 0·6 to 0·8 per cent. for extractives, the analyses in cases of carcinomata of different sites gave for urea less than 80 per cent., for uric acid 1 to 5 per cent., for NH_3 0·2 to 13 per cent., and for extractives 13 to 23 per cent. of nitrogen. These observations have been tested repeatedly by later observers, and have partly been confirmed.

1. Uric Acid.

By drawing an analogy with leuchæmia, Horbaczewski (134) tried to couple the relative increase of the uric acid, which he, too, observed in a case of cancer of the liver, with the leucocytosis of cancer. Cario (135), on the other hand, found an increase of uric acid in cancer of the œsophagus, where, as a rule, leucocytosis is absent. Brandenburg and Blumenthal (136), who determined the proportion between the nitrogen of all the alloxur bodies and the total nitrogen, obtained in the majority of cases abnormally high values. According to Blumenthal, this phenomenon is not specific for cancer, as it occurs also in other forms of cachexia, and disappears in cancer when the protein katabolism is temporarily arrested. That the relative increase of uric acid, which never attains any very high values, may be completely missing is further confirmed by the careful analyses of G. Setti (139).

2. Ammonia.

Positive results of an increased NH_3 excretion have been obtained by Töpfer, by von Noorden (138), and by von Limbeck (140), while decreased outputs have been recorded by Braunstein (141) and by Setti (139). To speak of it as a regular symptom is, therefore, out of the question. If it is marked, it must be associated with the advanced stage of inanition, or with the increase in the protein katabolism.

3. Extractives.

The relative increase of the nitrogen of the extractives seems to be the most regular change. In any case, Setti constantly found the figures for the extractive nitrogen to be high (higher than 10 per cent. of the total nitrogen), even in those cases where the values for uric acid and for NH_3 had remained normal. According to Setti, the proportion of the extractive nitrogen to the total nitrogen increases as the disease

advances. This change acquires a special significance by the fact that the proportion of urea nitrogen to the total nitrogen decreases *pari passu*. The causes for these disturbances are, however, still unknown.

B.—PERCENTAGE OF ASH.

1. NaCl.

Most investigators who analyzed the urine of cancer patients have been struck by the fact that the percentage of chlorine in the urine is frequently a very low one, especially when compared with the total nitrogen percentage (1, 135, 138, 142, 143). But this is not a constant occurrence—in fact, a temporarily increased excretion of NaCl may even take place (120, 139, 141, 144, 145). Beneke (146) tried to explain the low NaCl excretion by the cancerous constitution which, he alleged, is distinguished by a lack of alkaline chlorides, a view which it is unnecessary to discuss in the light of our present knowledge. According to von Noorden, it is due simply to a diminished intake of NaCl. "The higher the degree of inanition on the one hand, and of the breaking down of protoplasm on the other hand, the greater will be the disproportion between the percentage of nitrogen and chlorine in the urine. Such a condition is most easily established in cancer of the stomach and of the œsophagus, and it is just in such cases that the most striking differences between NaCl and nitrogen are found; while the normal proportions can be maintained in such cases of cancer where the pathological protein katabolism is not yet progressing too rapidly, and where a large intake of food entails the combustion of a comparatively large proportion of food protein and of a comparatively small proportion of tissue protein." But this explanation, too, is not valid for all cases. Laudenheimer's observations showed that simultaneously with the retention of NaCl there is a retention of water, so that chlorides and water are retained in almost the same proportion in which they occur in œdema or in the transudates of cancerous patients. This circumstance must, therefore, also be taken into account. For those cases which are associated with anæmia, Moraczewski has adduced evidence showing that the retention of NaCl depends to a certain extent on the anæmia itself.

2. Phosphoric Acid.

The excretion of phosphoric acid in cancer differs from the excretion of chlorides in being frequently, although by no means regularly, increased. This fact is easily explained if we can show that the decomposition of protein is also at the same time increased. In most cases the increase in the P_2O_5 excretion was actually found to be proportionate to the nitrogen excretion. But observations are on record by various authors, who found the ratio $P_2O_5 : N$—which for normal urine has the value 1 : 7—to be greater—*e.g.*, 1 : 3 to 1 : 5. If this is the case with badly-nourished, starving, or cachectic persons, we must infer that, in addition to the muscular substance, which contains $P_2O_5 : N$ in the proportion of 1 : 7, another tissue, richer in phosphorus, is undergoing disintegration.

This might be either glandular tissue, which is rich in nuclein, or osseous substance. The latter view seems more probable in the light of Lewin's work, to which we shall refer presently.

3. Sulphuric Acid.

Cario made determinations of the sulphuric acid in cases of cancer of the œsophagus, and found that its excretion runs parallel to that of the nitrogen. On two occasions he obtained figures which were disproportionately high, but was unable to give an explanation of this phenomenon.

4. The Total Mineral Constituents.

After the theory of demineralization in tuberculosis had been put forward, the question arose whether there was, in the cachexia of cancer, an analogous increase in the excretion of mineral salts as compared with the intake. Lewin investigated this question in eleven cancerous patients, and came to the conclusion that such a process actually takes place, even in cases with a positive nitrogen balance. Demineralization, however, according to this observer, is not a symptom characteristic of cancer, but rather a phenomenon associated with the most diverse forms of cachexia, occurring wherever there is a disintegration of tissue protein.

C.—HYDROBILIRUBIN.

F. Müller (148), as a result of his investigations on jaundice, states that the cachexia of cancer is generally accompanied by an increased excretion of urobilin. He bases his views upon the quantitative analyses made by Gerhardt (149), who observed the highest values in cases of cancer of the liver. Von Noorden (138) likewise found that in cancer of various organs the percentage of urobilin was frequently increased. Recently Braunstein (150) has repeated these investigations. He determined the amount of urobilin in the urine of twenty-two cancerous patients. He agrees with Gerhardt that exceptionally large quantities of urobilin are found in the urine of patients suffering from cancer of the liver, even if the bile-ducts are not obstructed. For the rest, he concludes that cancer of the various organs does not give rise to any marked signs of urobilinuria, but that this symptom may appear very readily when fever and putrefaction supervene. We have here another example of a symptom which is in no way specific for cancer, but which is evidently a secondary effect, dependent upon the destruction of the blood or upon the impairment of the function of the liver.

D.—PRODUCTS OF THE PUTREFACTION OF PROTEIN.

The putrefactive processes in the organism, especially those in the digestive tract, can be measured to a certain extent by the amount of ether-sulphuric acids, phenol, indican, and aromatic oxy-acids appearing in the urine. The question how far such an estimate is correct is dealt with in detail in the chapter on Intestinal Diseases. To judge from the

excretion of these substances, the putrefactive processes are considerably increased in cancer, especially in cancer of the digestive tract. A number of authors (1, 151 to 159) were able to demonstrate a periodically increased excretion of one or more of the substances mentioned above. The cause of this phenomenon was looked for in the readily putrefying secretions of the ulcerating tumour surface. This view is supported by the fact that putrid new growths of the mamma and of the uterus behave in this respect in the same way as tumours of the digestive tract. Quite recently Lewin (160) has protested against this assumption. He finds that cancerous patients with a negative nitrogen balance—in other words, with cachexia—show a much greater excretion of aromatic substances in the urine than do those with a positive nitrogen balance, and he assumes that the aromatic bodies, such as phenol, indol, and aromatic oxy-acids, are formed partly in the tissues themselves, resulting as a consequence of the toxogenous protein katabolism associated with the cachexia of cancer. That necessitates the assumption that these substances are intermediate products of the metabolism. He bases his views on the work of various observers, which is supposed to have proved the possibility of a direct formation of these substances. This question is, however, still too controversial to justify a practical application to the conditions obtaining in cancer, and, above all, the existence of an increased protein katabolism alone is not sufficient evidence whereon to establish an intermediate formation of even a part of the so-called putrefactive products.

E.—ACETONE, DIACETIC ACID, AND β-OXYBUTYRIC ACID.

Acetonuria and diaceturia frequently accompany the cachexia of cancer. The excretion of these substances is caused by the increased protein katabolism, and by the inanition which so frequently appears in the last stages of cancer. It stands in no relation to the growth of the cancer as such, because it is absent in the earliest stages, when the metabolism is still normal [von Jaksch (161), Klemperer (162), Thomas (163)].

There may even be an excretion of β-oxybutyric acid in the urine [Klemperer], especially in cases exhibiting the rather rare group of symptoms known as "coma carcinomatosum," which resembles in every respect the diabetic coma (164). In the coma of cancer the alkalinity of the blood is diminished, as it is in the coma of diabetes, and there is no doubt that in cancer, too, the cause must be looked for in acid intoxication. There is no evidence to show that this poisoning by acid is specific to cancer, as has been supposed. We cannot go into the details of this question here, and will only state that everything tends to show that in cancer it is produced by exactly the same conditions which give rise to it in diabetes.

F.—LACTIC ACID.

Von Noorden (138) found lactic acid in considerable quantities in the urine of two cancerous patients, but no significance is attached by him to this fact.

G.—PROTEINS AND ALBUMOSES.

According to F. Müller (1), albuminuria, which may only be temporary, appears in 35 to 72 per cent. of all cases of cancer. Albumoses are found in the urine with an almost equal frequency—at least, in cancer of the digestive tract [Ury and Lilienthal (165)]. Maixner (166) believed that the albuminuria was due to the direct absorption of the albumoses of the chyme by the ulcerated tumour surface (so-called " enterogenous peptonuria "), while Pacanowski (167) brings it into relation with the disintegration of the tissues within the tumour (histogenous origin). Most of the later investigators, especially Ury and Lilienthal, who have done a great deal of work on this subject, are inclined to agree with Pacanowski's view. This explanation appears all the more reasonable in view of the fact that Blumenthal has demonstrated the presence of albumoses in broken-down cancerous tissue (168).

H.—PEPTONES AND AMINO-ACIDS.

Wolff (180) was unable to find any peptones or amino-acids in the urine of cancerous patients.

I.—TOXICITY OF THE URINE.

Meyer (169) determined the toxicity of the urine of cancerous patients by Bouchard's methods, and found it to be markedly increased. With the onset of the coma, the toxicity suddenly fell to an unusually low value. Meyer has not attempted to separate the toxines in question.

A review of the facts here discussed does not reveal anything specific for the metabolism of cancer. A close inquiry into the relative increase in the NH_3 and in the extractive nitrogen, the retention of NaCl, the hydrobilinuria, the increased excretion of putrefactive products, etc., has shown that none of these phenomena can claim to be a characteristic feature of cancer. The same may be said of the albumosuria and of the increased toxicity of the urine. The true causes of these anomalies of the metabolism are to be found in the inanition, the febrile secondary infections, the destruction of the cancerous tissue and its putrefaction, and occasionally also in the impairment of important functions of organs such as the liver. In the next section we shall discuss whether, apart from these factors, there is any reason to assume the existence of a specific cancer ferment.

V.—IS THERE A SPECIFIC ACTION OF THE CANCER TISSUE ON THE METABOLISM ?

The breaking down of the tissue protein in cancer has always been looked upon as the main evidence in support of the view that a specific cancer toxine exists. This toxogenous katabolism of protoplasm, which manifests itself

clinically as emaciation and loss of strength, can be demonstrated in many cancer patients by examining the nitrogenous metabolism. But a critical survey of the literature has shown us that this breaking down is due in most cases to inanition, or to febrile secondary infections, or to a putrid secretion produced by the tumour surface. The few remaining observations which cannot be interpreted in this way have not established in a sufficiently conclusive manner the existence of a toxine responsible for the breaking down of the tissues. If we now turn to the anæmia of cancer, the other main factor in the cachexia of cancer, we meet with a similar case. All the arguments in favour of its specific nature have been found to be invalid; and although hæmolysins have been demonstrated in the blood of cancerous patients and in the cancer tissue, the proof for the existence of a specific toxine of the blood has still to be brought. We have seen, further, that all the symptoms on the part of the digestive organs, and all the abnormalities in the composition of the urine, can be completely accounted for by the secondary processes accompanying the development of cancer, which include, in addition to those mentioned above (inanition, infection, and excretion of disintegrated material), the impairment of the functions of important organs (stomach, liver, pancreas, bone-marrow, etc.).

We can readily understand Blumenthal (170), who in recent years has done a great deal of work on the cachexia of cancer, when he says: "A specific toxine of cancer, secreted by the cancer cells, and inducing in the metabolism of cancerous patients changes leading to cachexia, does not exist. All the changes in the metabolism which we can demonstrate have been called forth, on the one hand, by a diminished intake of food; on the other hand, by secondary diseases of organs which play an important part in metabolism; and lastly, by increased bacterial processes."[1]

Nevertheless, it must be admitted that these explanations are somewhat unsatisfactory. There are examples available of cancerous cachexia without any inanition, without any infection, or without any disintegration of the cancerous tissue. In fact, every patient who has cancer without complications, even those who for some time fail to show any signs of protein katabolism, become cachectic in the end. Further, if the cancer cells do not secrete a toxine, how can we explain the atrophy of the surrounding tissues, which proceeds together with the growth of the tumour? It can hardly be assumed that the normal tissue is destroyed simply by the mechanical pressure of the proliferating tumour tissue. We know that healthy cells offer a very strong resistance to mechanical injuries. It seems, perhaps, more reasonable to assume that the cancerous tissue

[1] This view is confirmed by the work of Clowes, Frisbie, and Glosser (186), who failed to find such extensive disturbances of the metabolism as those observed by Müller and Moraczewski. They doubt that the cachexia of cancer is produced by toxines, and are inclined to believe that the greater part of the disturbances of the metabolism are due to an insufficient oxidation of the nitrogenous products of the metabolism. Quite recently von Hansemann (187), who formerly held that the cachexia of cancer was an essential feature of the disease, related to the anaplasia of the cells, has abandoned his standpoint in view of the pathological and experimental evidence. He states definitely that "cancer, as such, does not produce cachexia. In the majority of cases the anæmia and emaciation are due to factors accompanying cancer." It is interesting to note that this conclusion was arrived at by Sir Samuel Wilks forty years ago, on the basis of 2,000 autopsies in Guy's Hospital (188).

weakens the normal cells by depriving them of their nourishment. But then we should find a positive instead of a negative nitrogen balance. No matter how we argue, we always find ourselves postulating that the cancer cells exert a chemical influence on the normal tissue.

There is one fact in the pathology of the metabolism of cancer which tends to support such a view, and indicates the way in which such a chemical influence might be brought about; that is the observation of Emerson (24), that in cases of gastric cancer the tumour tissue contains a ferment capable of aiding the digestion of protein both in artificial digestive mixtures and in the gastric contents. Whether this ferment is a specific cancer ferment, or belongs to the autolytic ferments common to all tissues, remains an open question. In the body it passes into the gastric contents from the ulcerated or excoriated tumour surface. It is, therefore, not a secretion; at any rate, there is no evidence to show that it diffuses out from the intact surface of cancerous tumours, or that it is absorbed into the circulation. It exists most probably already in the living cells, for Emerson used fresh cancerous tissue in his experiments *in vitro*. That the active substance was a ferment was proved by the fact that the protein substances were not digested if the cancerous tissue had been boiled previously.

The results of these highly interesting experiments direct attention to the chemistry of the cancerous tissue. Petry (171) was the first to investigate the subject more closely. He found the tumour tissue to be rich in nucleo-albumin—a fact which he ascribes to the nuclei being comparatively numerous. In addition, his observations show a remarkably rapid autolysis of the tumour tissue *in vitro*. Even at room temperature a large percentage of the protein substance of the sterile tumour tissue was transformed in a very short time into non-coagulable substances which had already passed the stage of albumoses. Normal tissue underwent these changes much later, and not to the same extent. Similar observations were made by H. Wolff (172) and by Beebe (173). The former found that, as compared with normal tissues, the cancerous tumours are very poor in globulins, but relatively rich in albumins, and that the melanin of a melanotic sarcoma which he examined was not identical with the melanin which is normally present in the body (the melanin in the eye), but that it is a peculiar substance of a different composition. Beebe observed nucleohiston to be a constituent of rapidly growing tumours of lymphatic glands. As yet, the number of such investigations is very small, but their results are sufficient to show that the chemical composition of the cancerous tissue may sometimes differ from that of normal tissues.[1]

[1] Beebe (189) made careful analyses of the inorganic elements in a number of malignant new growths. In degenerated tumours the calcium was found to be increased in amount; these tumours showed also a relative deficiency of potassium salts. The amount of pentose in cancer, to which Neuberg had drawn attention, was investigated by Beebe and Shaffer (190). They found it to be higher in cancer of the breast than in normal mammary tissue. The same result was obtained in cases of scirrhous cancer of the breast, so that this phenomenon cannot be due to the cancerous tissue being rich in nuclei, as Neuberg supposed. It is very difficult, as Beebe himself recognises, to draw general conclusions from the results of isolated analyses of various tumours, growing under different conditions and having reached different stages of their development when they are submitted to examination.

In any case, the marked autolysis of cancerous tissue is of great importance, and the most recent investigations have accordingly been made in this direction. Neuberg and Milchner (174) observed the appearance of pentose in the tissue of metastatic growths from the liver which had undergone autolysis; pentose is not found in the normal liver tissue. Neuberg (175) continued these investigations later by working out the autolytic products of the primary carcinoma of the stomach from which these metastatic new growths had arisen. He found that the primary tumour yielded none, or at any rate very much less pentose on autolysis, although on hydrolysis it was found to contain a considerable amount of pentose. The migration of the tumour cells from the primary site either induces a variation of their ferments, or they acquire new fermentative properties. Further, if the juice of the tumour of the liver is allowed to act on the proteins of the lung, an extensive decomposition of the lung protein is brought about. The cancer ferment acts, therefore, not only autolytically, but also "heterolytically," to use a term proposed by Jacoby (176). The heterolytic action differs in kind and in degree from the action of the autolytic ferments of the normal liver. With slightly different experimental conditions, Blumenthal and Wolff (177) arrived at the same conclusion—namely, that a heterolytically acting ferment exists in the cancerous tissue. When they autolyzed two pieces of liver tissue, to one of which a small piece of a cancer of the breast had been added, they observed that the autolysis was much more rapid in the tube containing the tumour tissue. At the same time, these two observers found that the cancer tissue sometimes resists the action of pepsin-hydrochloric acid, while it is always equally affected by trypsin. Lastly, we may mention here Neuberg's (178) observations on the action of radium on the cancer tissue. Under the influence of radium, the cancer tissue became more quickly disintegrated than any other tissue, and the fermentative processes were affected in some peculiar manner. These recent results of cancer research are not yet based on sufficiently numerous observations to allow us to draw far-reaching conclusions from them, but they throw light on many hitherto obscure processes in the pathology of cancer metabolism. It is now beyond all doubt that the fermentative action of gastric cancer on the protein substances of the gastric contents observed by Emerson is a heterolytic process. It follows from this that not only does the cancerous tissue, after being removed from the body, undergo an extraordinarily rapid disintegration by autolysis, but its autolytic ferment is capable of accelerating the autolysis of other organs. Having arrived at this conclusion, we are at once confronted with an abundance of new problems, of which only the most obvious ones may be mentioned here. Is the autolytic ferment already present in the living cells, or is it only being formed at the death of the cells? In the living organism, does it enter into the circulation from the cancer tissue? Does it exercise its heterolytic effect also on the living tissues?

It is to be hoped that the rapid advances in cancer research will soon solve these questions. Until then it would be futile to indulge in speculation. We only wish to emphasize here once more that the autolytic ferment of cancer, the existence of which has been demonstrated, should

on no account be identified at present with the hypothetical toxine of cancer. Autolytic ferments are present also in normal tissues, and they are often very active in disease—*e.g.*, in pneumonia. That they occur in cancer so copiously, and at a very early stage, is due to the fact that the cancerous tissue is very liable to degeneration and decay, especially when its rapid growth has resulted in a defective vascularity. The existence of the autolytic ferment certainly helps to explain many features of the metabolism of cancer, but in itself it does not account for the cachexia, not even in virtue of its heterolytic quality. The identity of the ferment with the toxine postulated for cancer can only be accepted as established when it has been shown that the ferment of cancer is secreted by the living cancer cells, enters the circulation, and by its heterolytic action breaks down the healthy tissues.

ADDENDUM.

Some Problems of the Metabolism of Cancer from the Standpoint of Experimental Cancer Research.

By W. Cramer, Ph.D.D.Sc.

The recent development of experimental cancer research is likely to bring many of the controversial problems of the metabolism of cancer within the scope of methods of investigation which are free from the fallacies inherent in observations on clinical cases. The first step in that direction was made by Bashford and Cramer (1) with the material of the Imperial Cancer Research Fund.

Mice in which Jensen's tumour had been successfully transplanted were killed after a test meal, and the total acidity of the gastric contents was determined in a series of ten mice. Control estimations were made with a series of normal mice of the same age, which had been kept under the same conditions. It was found that the total acidity of the gastric contents of cancer mice was not only not less than that of normal mice, but even slightly higher.

More extensive observations on the same material were made by Copeman and Hake (2). Through the courtesy of Dr. Copeman, I am enabled to give a summary of their unpublished results. These two observers determined the physiologically active HCl and the organic acids in the watery extracts of the stomachs and stomach contents of over 500 mice, both cancerous and normal. They found that on the average there is a decided increase of physiologically active HCl in the stomach wall and gastric contents of cancer mice as compared with normal mice, the increase amounting in some cases to as much as 50 per cent. The increase was as marked with ulcerated tumours as with non-ulcerated tumours.

In order to fully appreciate the significance of these facts, it must be remembered that in mice suffering from experimental cancer the con-

ditions are essentially different from those obtaining in man, where the changes connected with the primary cancerous transformation of a few cells are combined with secondary changes accompanying the subsequent growth of those cells. Bashford and Murray (3, 4) were the first to point out that the conditions governing the origin of cancer are altogether different from those governing its growth, and Ehrlich and Apolant (5) have subsequently arrived at the same conclusion. This view is based mainly on two facts: tumours arise, as a rule, in old animals, while young animals provide a much more favourable soil for their subsequent growth. Cancer occurs naturally once in 1,500 to 3,500 mice. Nevertheless, the great majority of the animals in which it is so rare naturally can be inoculated successfully. When mice are made to suffer from experimental cancer, the cancer cells grow in and act upon an otherwise normal organism. The investigations of Copeman and Hake show that such a symbiosis leads to a definite chemical change—namely, an increase in the chlorides of the stomach wall and stomach contents of the organism which serves as a host for the cancer cell. Whether this phenomenon is connected in any way with the decrease of HCl observed clinically in man remains an open question.

Clowes and Frisbie (6) have made careful chemical analyses of the mineral salts in a number of artificially propagated mouse tumours. They find that healthy, rapidly-growing tumours are comparatively rich in potassium, while necrotic tumours show a relative abundance of calcium. The deposition of calcium salts in dead or necrotic tissues is a common pathological process, and these observations fail to reveal anything specific to cancer.

Unfortunately, up to now the only animal found to be suitable for the artificial propagation of cancer on an extensive scale has been the mouse, so that metabolism experiments have not yet been possible. Nevertheless, a condition comparable with the cachexia of the human subject can be easily recognised in some of the animals experimented upon. Observations on 3,000 cancer mice [Bashford, Murray, and Cramer (7)] have shown that the presence of a tumour, however great, does not necessarily lead to a cachectic condition. On the contrary, the animals appear quite healthy and active, and on necropsy are found to possess an abundance of fat. When, however, the integument covering the tumour ruptures, the hæmorrhage and septic infections which follow speedily produce marked constitutional effects. The same condition is produced if the walls of the alimentary canal become the site of growths after a successful intraperitoneal inoculation, or if rapid metastasis formation takes place, involving the internal organs, such as the liver. It follows from this that the cachexia stands in no essential relation to cancer, of which it is only an occasional accompaniment.

The experimental propagation of cancer has thrown light on another controversial question [Bashford, Murray, and Cramer (7, 8)]. Under experimental conditions, no essential difference exists between the benign or expansive, and the malignant or infiltrative, forms of growth. In considering malignant new growths, the benign tumours must not be omitted. A tumour which, after subcutaneous transplantation, grows

without infiltrating the surrounding tissues may, after intraperitoneal transplantation, exhibit all the typical features of malignancy, infiltrating the organs to which it has become attached. When such a tumour is transplanted again subcutaneously, it does not possess greater infiltrative power than others. Therefore the apparently enhanced malignancy after intraperitoneal transplantation does not indicate an alteration in the character of the tumour. If the more destructive effect of infiltrating growth were due to a digestive action of a ferment, it is difficult to understand why the same mode of growth should be less marked after subcutaneous transplantation. Besides, microscopical examination of infiltrating tumours, sporadic and transplanted, fails to give any evidence of a digestive action, and points rather to the importance of mechanical hindrances to growth. The malignancy of a tumour is merely a manifestation of its power of growth under given anatomical conditions. As it can be varied experimentally in one and the same tumour by allowing it to grow in different sites, the malignancy cannot be solely dependent upon characters inherent in the tumour cells.

The results of experimental cancer research bearing on metabolism may be summed up, according to Bashford, Murray, and Cramer, as showing definitely that all the attributes of cancer are but the consequences of its growth, which is its only constant property. Growth, again, is dependent upon the assimilation of food, and Ehrlich (9, 10) has gone so far as to postulate an increased avidity for food-stuffs on the part of the " receptors " of cancerous cells as compared with normal cells. The increasing frequency of cancer as age advances—which, as Bashford (11) has shown, is a constant feature of the disease in all the vertebrates, whether life be short or long—is explained by Ehrlich as due to a diminution in the vital function of the organism as a whole. The experimental investigation of cancer has not produced any evidence in favour of the existence of a specific cancer toxine. But it has shown that cancer affects the organisms in which it grows by virtue of the increased nutritive capacity of the cancer cells.

LITERATURE.

1. Müller : Stoffwechselunters. bei Krebskranken. Z. M. **16.** 496. 1889.
2. Van der Velden : Ueber Vorkom. u. Mangel der freien Salzsäure im Mageninhalt. D. Ar. M. **23.** 369. 1879.
3. Wagner : Chem. Funktionsprüf. des Magen. Ar. V. **11.** 1. 1905.
4. Richter : Ü. Salzsäureabscheid. beim Magenkarzinom. Ibid. **5.** 379. 1900.
5. Rosenheim : Ueber einige oper. behandelte Magenkranke nebst Bemerk. ü. Milchsäuregärung. D. m. W. **95.** 238, 260; Zur Kenntnis des mit Krebs kompl. runden Magengeschwürs. Z. M. **17.** 116. 1890.
6. Schneider : Ü. die HCl-Sekret. u. Resorptionsfäh. der Magenschleimhaut bei den versch. Magenkrankh. u. anderweitigen krankhaften Zuständen. Ar. p. A. **148.** 243. 1897.
7. Riegel : Die Erkrank. des Magens. Nothnagel's Handb. der spec. Path. u. Ther.
8. Cahn u. Mehring : Die Säuren des gesunden und kranken Magens. D. Ar. M. **39.** 233. 1886.

9. Honigmann u. v. Noorden: Ueber HCl im karzinomatösen Magen. Z. M. **13.** 87. 1888.
10. Martius u. Lüttke: Die Magensäure des Menschen. 1892. P. 155.
11. Rosenheim: Ü. atroph. Prozesse an der Magenschleimhaut in ihrer Beziehung zum Karzinom und als selbständige Erkrankung. B. k. W. **1888.** 1021.
12. Hammerschlag: Über das Magenkarzinom. Ar. V. **2.** l, 189. 1896.
13. Rosenheim: loc cit. (Nr. 5). D. m. W. **1895.** 238.
14. Bourget: Ü. den klin. Wert des Chemismus des Magens. T. M. **1895.** 221.
15. v. Noorden: Stoffwechsels. 1893. P. 460.
16. Boas: Diag. u. Ther. der Magenkrankh. 1890. P. 138.
17. Riegel: Beitr. zur Lehre von den Störungen der Saftsekret. des Magens. Z. M. **11.** 1. 1886.
18. Moore, Alexander, Kelly and Roaf: On the Absence or Marked Diminution of Free HCl in Gastric Contents in Malig. Disease of Organs other than Stomach. Fifth Ann. Rep. Cancer Labor., N. York State Depart. of Health. 1903-1904.
19. Zjenez: Zur Diag. des Karzinoms der Verdauungsorgane. W. **1899.** 8. Ar. V. **5.** 392. 1900.
20. Riegel: Path. u. Diag. der Magenkrankh. D. Ar. M. **36.** 100. 1885.
21. Reissner: Ueber das Verhalt. des Chlors im Magen u. d. Ursache des HCl-Mangels bei Magenkrebs. Z. M. **44.** 71. 1902.—Warum fehlt beim Magenkrebs die freie HCl? K. i. M. **19.** 310. 1901.
22. v. Tabora: Zur Path. des Magenkarzinoms. D. m. W. **1905.** Nr. 15, 16.
23. Clowes and Jeffcot: See Nr. 18; also Bi. C. **3.** 1905. Nr. 23.
24. Emerson: Der Einfl. des Karzinoms auf die gast. Verdauungsvorgänge. D. Ar. M. **72.** 415. 1902.
25. Salomon: Zur Diag. des Magenkarzinoms. D. m. W. **1903.** July 30.
26. Orlowski: Zur Diag. des Magenkarzinoms. W. **1904.** 24. Ar. V. **11.** 103. 1905.
27. Sigel: Zur Diag. des Magenkarzinoms. B. k. W. **1904.** Nrs. 12 and 13.
28. Berent u. Gutmann: Ü. vermehrten N- und Eiweissgeh. der Magenflüssigkeit u. seine diag. Bedeutung. D. m. W. **1904.** Nr. 28.
29. Pstrokonski: Ein primäres Sarkom des Magens. Dunin's Festschr. 1901. Ar. V. **8.** 354. 1902.
30. Schorlemmer: Über die Grösse der eiweissverdauenden Kraft, etc. Ar. V. **8.** 299, 487. 1901.
31. Oppler: Verhalt. des Pepsins bei Erkrankungen des Magens. Ibid. **2.** 40. 1896.
32. Glaessner: Zur topischen Diag. der Magengeschwülste. B. k. W. **1902.** Nr. 29.
33. Rosenberg: Ueber den Umfang der Eiweissverd. im menschl. Magen. Z. M. **56.** 449. 1905.
34. Boas: Eine neue Meth. der qualit. u. quant. Milchsäurebestim. im Mageninhalt. D. m. W. **1893.** Nr. 34.—Ü. das Vorkommen von Milchsäure im gesunden und kranken Magen nebst Bemerk. zur Klin. des Magenkarzinoms. Z. M. **25.** 85. 1894.
35. Ekehorn: Statistik der Bedeut. und des Vorkommens der Milchsäuregärung beim Magenkarzinom. Ar. V. **3.** 107. 1898.—Noch einige Fälle von Magenkarzinom mit besonderer Berücksichtigung der Milchsäurereaktion. Ibid. **3.** 361. 1898.
36. Strauss: Ueber Magengärungen. Z. M. **26.** 514. 1894.
37. De Jong: Der Nachweis der Milchsäure. Ar. V. **2.** 53. 1896.
38. Buhre: Die Bedeut. der Milchsäurereak. für die Diag. des Magenkrebses. Ar. V. **3.** 361. 1898.
39. Chiaruttini: Ueber den diag. Wert der Milchsäure beim Magenkarzinom. G. O. **1898.** Nr. 55. Ma. **1898.** 328.
40. Seelig: Die diag. Bedeut. der Milchsäurebest. nach Boas. B. k. W. **1895.** Nr. 5.
41. Boas: Diag. u. Ther. der Magenkrankh. 1903. P. 216.
42. Klemperer: Über den Stoffw. und die Ernähr. in Krankheiten. Z. M. **16.** 581. 1889.
43. Malassez: Sur la richesse du sang en glob. rouges chez les cancéreux. Pro. mé. **1884.** Nr. 28.
44. Sörensen: Undersogelser om Antallet of rode og hvide Blodlegemer under forskjellige physiol. og pathol. Tilstande. 1876.

45. Laache: Die Anämie. 1883.
46. Müller: Verhandl. des Vereins f. inn. Med. **1888.** 378.
47. Schneider: Das morph. Verhalt. des Blutes bei Herzkrankh. u. bei Karzinomen. Diss. Berl., 1888.
48. Daland u. Sadler: Ü. das Vorkommen der roten und weissen Blutkörperchen im Blute. F. M. **1891.** Nr. 20.
49. Mouisset: Carcinome de l'estomac. Ré. M. **1891.**
50. Osterspey: Die Blutuntersuch. u. ihre Bedeut. bei Magenkrankh. Diss. Berl., 1892.
51. Limbeck: Klin. Path. des Blutes. Jena, 1892.
52. Neubert: Stoffwechselunters. bei Krebskranken. Diss. Dorpat, 1889.
53. Strauer: Systemat. Blutunters. bei Schwindsüchtigen u. Krebskranken. Z. M. **24.** 295. 1894.
54. Henry: Ü. den diag. Wert der Blutkörperchenzählung beim latenten Magenkrebs. Ar. V. **4.** 1. 1898.
55. Rencki: Die diag. Bedeut. der Blutunters. bei Karzinom u. Ulcus ventric. rotundum mit besonderer Berücksichtigung der Verdauungsleukozytose. Ar. V. **7.** 234, 392. 1900.
56. Krokiewicz: Das Verhalten des Blutes im Verlaufe von Magenkarzinom. Ar. V. **6.** 25. 1900.
57. Laker: Die Bestim. des Hämoglobingeh. im Blute. W. m. W. **1886.** Nrs. 18-20.
58. Lubarsch: Hyperplasie und Geschwülste. 1895.
59. Leichtenstern: Über den Hämoglobingeh. des Blutes. 1878. P. 84.
60. v. Noorden: Stoffwechsel. 1893. P. 461.
61. Grawitz: Klin. Path. des Blutes. 1902. P. 627.
62. Jez: Ueber die Blutunters. bei Magenerkrankungen, besonders bei Ulcus u. Carcinoma ventric. W. m. W. **1898.** Nrs. 14, 15.
63. Schur u. Loewy: Ueber das Verhalt. des Knochenmarkes in Krankh. und seine Beziehungen zur Blutbildung. Z. M. **40.** 412. 1900.
64. Lang: Ueber die Resistenz der roten Blutkörperchen gegen hypoisoton. NaCl-Lösungen beim Magenkrebs. Z. M. **47.** 153. 1902.
64a. Devoto: Ueber die Dichte des Blutes, etc. Prag. Zt. **11.** 176.
65. Schmaltz: Die Untersuch. des spezif. Gewichts des menschl. Blutes. D. Ar. M. **47.** 145. 1891.
66. Peiper: Das spezif. Gewicht des menschl. Blutes. C. k. M. **1891.** 217.
67. Scholkoff: Spezif. Gewichts des Blutes, etc. Diss. Bern, 1892.
68. Grawitz: l. c. (No. 61). P. 626.
69. Boas: Diag. u. Ther. der Magenkrankh. 1903. P. 298.
70. Häberlin: Ueber den Hämoglobingeh. des Blutes beim Magenkrebs. Mü. m. W. **1888.** Nr. 22.
71. Engelsen: Diss. Kopenhagen.
72. Eichhorst: Spez. Path. u. Ther. **2.**
73. v. Jaksch: Zur Chem. des Blutes. K. i. M. **12.** 236. 1893.
74. Wendelstadt u. Bleibtreu: Beitr. zur Kenntnis der quant. Zusammensetz. des menschl. Blutes unter pathol. Verhält. Z. M. **25.** 204. 1894.
75. Stintzing u. Gumprecht: Wassergeh. und Trockensubst. des Blutes. D. Ar. M. **53.** 265. 1894.
76. Boas u. Kochmann: Okkulten Magenblutungen. Ar. V. **8.** 45. 1902.
77. Grawitz: l. c. (61). P. 629.
78. Micheli u. Donati: Sulle proprietà emolitichi degli estratti di organi e di tumori maligni. R. M. **1903.** Nr. 8.
79. Kullmann: Ueber Hämolyse durch Karzinomextrakte. B. k. W. **1904.** Nr. 8.
80. Bard: De l'hémolyse dans les liquides hémorr. d'origine cancéreuse. Se. m. **1901.** Nr. 25.
81. Virchow: Cellularpathol. 1872.
82. Escherich: Hydrämische Leukozytose. B. k. W. **1884.** 145.
83. Eisenlohr: Blut und Knochenmark bei progr. perniziöser Anämie u. bei Magenkarzinom. D. Ar. M. **20.** 495. 1877.
84. Potain: Un cas de leucocythémie. Ga. h. **1888.** Nr. 57.
85. Schaper: Blutuntersuchungen, etc. Diss. Göttingen, 1891.
86. Reinert: Zählung der roten Blutkörperchen. 1891. P. 208.

87. Muir: Phys. and Path. of Blood. J. A. and P. **25.** 1891.
88. Alexander: De la leucocytose dans les cancères. 1887.
89. Strauss u. Rohnstein: Die Anämien. 1901.
90. Rieder: Beitr. zur Kenntnis der Leukozyten. 1892. P. 95.
91. Einhorn: Ueber das Verhalt. der Lymphozyten zu den weissen Blutkörperchen. Diss. Berl., 1901.
92. Reinbach: Ü. das Verhalten der Leukozyten bei malig. Tumoren. Ar. k. C. **46.** 486. 1893.
93. Feldbausch: Ü. das Vorkom. von eosinop. Zellen in Tumoren. Ar. p. A. **161.** 1. 1900.
94. Schneyer: Das Verhalt. der Verdauungsleuk. beim Carcinoma ventric. und Ulcus rotund. I. R. **1894.** Nr. 39.
95. Hofmann: Die Verdauungsleuk. beim Carcinoma ventric. Z. M. **33.** 460. 1897.
96. Sailer and Taylor: Internat. M. Mag. **1897.** July.
97. Japha: Verdauungsleukozytose. D. Z. **1901.** Nr. 7. Ar. V. **8.** 171. 1902.
98. Dolmatow: Über den diag. Wert der Verdauungsleukozytose bei Magenkarzinom. Russ. milit.-med. Ztg. **5.** 1899. Ar. V. **6.** 90. 1900.
99. Douglas: Digestion leucocytosis in Cancer of the stomach. B. M. J. **1901.** March 16.
100. Machetti: Das Verhalt. der Verdauungsleukozy. bei verschied. Krankh. M. **1896.** Hft. 10.
101. Donati: Das Blut von Individuen mit malignen Geschwülsten. Ac. T. May to July, 1901. Ma. **1901.** 183.
102. v. Jaksch: Alkaleszenz des Blutes in Krankh. Z. M. **13.** 1888.
103. Peiper: Alkalimet. Untersuch. des Blutes. Ar. p. A. **116.** 337. 1889.
104. Rumpf: Alkalimet. Untersuch. des Blutes. C. k. M. **1891.** 441.
105. Klemperer: CO_2-Gehalt des Blutes bei Krebskranken. Ch.-An. **15.** 1890.
106. Strauss: Blutalkaleszenz des Menschen. Z. M. **30.** 317. 1896.
107. Orlowski: Alkaleszenz des Blutes. P. L. **40.** 241. 1901. Ma. **1901.** 264.
108. v. Moraczewski: Stoffwechselvers. bei Karzinom und Chlorose. Z. M. **33.** 385. 1897; Ueber den Cl- und P-Gehalt des Blutes bei Krebskranken. Ar. p. A. **139.** 385. 1895.
109. Freund: Zur Diag. des Karzinoms. W. m. B. **1885.** Nrs. 9, 36.
110. Trinkler: Ueber die diag. Verwertung des Gehaltes an Zucker im Blute. C. m. W. **1890.** 486.
111. Matrai: Chem. Unters. des Blutes bei Krebskranken. Pest. m.-chir. Presse. **1885.** Nr. 36.
112. Achard u. Clarc: Pathol. Schwankungen des amyloly. Vermögens des Blutserums. C. r. S. B. **53.** 708. 1901.
113. Israel: Ueber funktion. Nierendiag. G. M. C. **11.**
114. Engelmann: Beitr. zur Lehre von dem osmot. Druck u. der elek. Leitfähigkeit der Körperflüssigk. Ibid. **12.**
115. Engel: Ueber die Gefrierpunktserniedrigung des Blutes bei Krebskr. B. k. W. **1904.** 828.
116. Ascoli: Isoagglut. und Isolysine menschl. Blutsera. Mü. m. W. **1901.** 1239.
117. Kreibisch: Ueber einige serodiagnost. Versuche. W. k. W. **1902.** Nr. 27.
118. v. Noorden: l. c. (60). P. 456.
119. Ibid. P. 155.
120. Gärtig: Stoffwechselunters. in einem Falle von Œsophaguskarzinom. Diss. Berl., 1890.
121. Klemperer: Stoffwechselvers. an Krebskranken. Ch.-An. **16.** 138. 1891.
122. Widal: Hypoazoturie et sa signification. Arch. prov. de méd. **1899.** March. Ar. V. **5.** 540. 1899.
123. Setti: Ü. die Aussch. des N, der Chloride u. d. Phosphate u. die Verteil. des N unter die versch. N-haltigen Bestandteile des Harns beim Karzinom. R. v. **16.** 31. 1899. Ma. **99.** 741.

124. Braunstein: Über die Aussch. der Chloride, der Phosphorsäure, des N, u. des NH_3 beim Karzinom. Zt. f. Kerbsf. **1.** 199. 1904.

125. Clowes, Frisbie, and Glosser: Studies on Cancer Metab. See No. 18. Bi. C. **3.** Nr. 23. 1905.

126. Moraczewski: Stoffwechselvers. bei Karzinom und Chlorose. Z. M. **33.** 385. 1897.

127. Lewin: Stoffwechselunters. bei Karzinomatösen. D. m. W. **1905.** 6.

128. Kraus u. Chvostek: Ueber den Einfl. von Krankh. aus den respirat. Gaswechsel. W. k. W. **1891.** Nr. 33.

129. Jaquet u. Svenson: Zur Kenntnis des Stoffwech. fettsüchtiger Individuen. Z. M. **41.** 375. 1900.

130. Freudweiler: Ein Beitr. zur Kennt. des Lymphosarkoms. D. Ar. M. **64.** 544. 1899.

131. Blumenthal: Zur Frage der Krebskachexie. Salkowski Festschr. 1904. P. 75.

132. Müller: Allge. Path. der Ernährung, in v. Leyden's Handb. der Ernährungsther. 1903. P. 224.

133. Töpfer: Relation. der N-haltigen Bestandteile im Harn bei Karzinomen. W. k. W. **1892.** Nr. 49.

134. Horbaczewski: Beitr. zur Kennt. der Bildung der Harnsäure. S. W. A. **1891.** 38.

135. Cario: Ü. den Einfl. des Fiebers und der Inanition auf die Aussch. der Harnsäure, etc. 1888.

136. Brandenburg: B. k. W. **1896.**

137. Blumenthal: Ueber das Verhält. der Aussch. des Alloxurkörper-N zum Gesamt-H beim Karzinom. Ch.-An. **21.** 144. 1896.

138. v. Noorden: l. c. (60). P. 464.

139. Setti: Ueber die Ausscheid. des N, der Chloride und der Phosph., und die Verteil. des N des Harnes beim Karzinom. R. v. **16.** 31. 1899. Ma. **1899.** 741.

140. v. Limbeck: Beitr. zur Lehre von der Säurevergiftung. Z. M. **34.** 419. 1898.

141. Braunstein: l. c. (124).

142. Sticker u. Hübner: Wechselbezieh. zwischen Sekreten und Exkreten. Z. M. **12.** 114. 1887.

143. Stroh: Anomalien der Cl-Aussch. bei Magenkranken. Diss. Giessen, 1888.

144. Schöpp: Ü. die Aussch. der Chloride bei Karzinomatösen im Verhältnis zur Aufnahme derselben. D. m. W. **1893.** Nr. 46.

145. Laudenheimer: Die Aussch. der Chloride bei Karzinomatösen. Z. M. **21.** 513. 1892.

146. Beneke: Path. des Stoffwech. 1874. P. 61.

147. Lewin: Stoffwechselunters. bei Karzinomatösen. Mü. m. W. **1905.** 47.

148. Müller: Ueber Ikterus. V. s. G. 1892.

149. Gerhardt: Ueber Hydrobilirubin. Diss. Berl., 1889.

150. Braunstein: Ueber den Nachweis des Urobilins u. seine Aussch. bei Karzinom. Zt. f. Krebsforsch. **1.** 15. 1903.

151. Brieger: Phenolaussch. bei Krankheiten. Z. p. C. **2.** 241. 1871.—Ueber einige Beziehungen der Fäulnisprod. zu Krankh. Z. M. **3.** 461. 1881.

152. Senator: Indikan und Kalkaussch. C. m. W. **1877.** 357, 370, 388.

153. Ortweiler: Ueber die phys. u. path. Bedeut. des Harnindikans. Mit. W. **2.** 153. 1885.

154. Hennige: Die Indikanaussch. in Krankh. D. Ar. M. **23.** 271. 1879.

155. Hoppe-Seyler: Ueber die Aussch. der Aetherschwefelsäuren im Urin. Habilitationsschr. Keil, 1887.

156. Leo: Die Krankh. der Verdauungsorgane. 1890. P. 316.

157. Häberlin: Neue diag. Hilfsmittel bei Magenkrebs. D. Ar. M. **45.** 339. 1890.

158. Wasbutzki: Einfl. der Magengärungen auf die Fäulnisvorgänge im Darm. Ar. P. P. **26.** 133. 1889.

159. Strauss u. Philippsohn: Ueber die Aussch. enterogener Zersetzungsprod. im Urin bei konstanter Diät. Z. M. **40.** 369. 1900.

160. Lewin: Aussch. der aromat. Substanzen im Urin bei Krebskranken. Festschr. f. Salkowski. 1904. P. 225.

161. v. Jaksch: Ueber Azetonurie und Diazeturie. 1885. P. 84.
162. Klemperer: Ueber den Stoffw. und das Koma der Krebskranken. B. k. W. **1889.** Nr. 40.
163. Thomas: See Neubauer-Vogel's Harnanalyse. 1890. P. 195.
164. On Coma carcinomatosum, see v. Jaksch: Über Azetonurie und Diazeturie. K. i. M. **2.** 269. 1883.—Riess: Ueber das Vorkommen eines dem sog. Coma diabet. gleichen Symptomenkomplexes. Z. M. **7.** 34. Suppl. 1884.—Senator: Ueber Selbstinfek. durch abnorme Zersetzungsvorgänge. Ibid. **7.** 325. 1884.—Klemperer: l. c. (162).
165. Ury u. Lilienthal: Ueber Albumosurie bei Magen-Darmerkrankungen, spez. Karzinomen. Ar. V. **11.** 72. 1905.
166. Maixner: Ueber eine neue Form der Peptonurie. Z. M. **8.** 234. 1884.
167. Pacanowski: Ueber die Peptonurie vom klin. Standpunkte aus. Z. M. **9.** 429. 1885.
168. Blumenthal: Verhandl. des Komitees für Krebsforschung. Sitz. vom May 14, 1904.
169. Meyer: Ueber die Toxiz. des Urins und Milzextraktes bei Karzinom. Z. M. **33.** 563. 1897.
170. Blumenthal: Zur Frage der Krebskachexie. Festschr. f. Salkowski; D. m. W. **1904.** Nr. 40.
171. Petry: Ein Beitr. zur Chem. maligner Geschmülste. Z. p. C. **27.** 398. 1899; Be. P. P. **2.** 94. 1902.
172. Wolff: Chem. des Karzinoms. Zt. f. Krebsforschung. **3.** 1905; Melanot. Pigmente. Be. P. P. **5.** 476. 1904.
173. Beebe: Chem. of Malignant Growths. A. J. P. **13.** 143. 1905.
174. Neuberg u. Milchner: Ueber das Verhalt. der Kohlenhyd. bei der Autolyse und zur Frage nach der Bindung der Kohlenhydratgruppe in Eiweisskörpern. B. k. W. **1904.** 1080.
175. Neuberg: Chem. zur Karzinomfrage. B. k. W. **1905.** Nr. 5.
176. Jacoby: Be. P. P. **3.** 446. 1903.
177. Blumenthal u. Wolff: Ueber Fermentwirk. bei Krebsgeschwülsten. M. K. **1905.** Nr. 7.—Blumenthal: Ueber Fermentwirk. bei Krebsgeschwülsten. D. m. W. **1905.** Nr. 7; Ueber die Ursachen der Malignität der Geschwülste. M. K. **1905.** Nr. 15.
178. Neuberg: Neues zur Karzinomfrage. Zt. f. Krebsforsch. **2.** 1905; **2.** 171. 1904; Ueber Radiums bei Karzinom. Verhandl. d. D. path. Ges. **1904.** 157.
179. Klemperer: K. i. M. **8.** 404. 1889.
180. Wolff: Zur Chemie der Krebsgeschwülste. M. K. **1905.** Nr. 13.
181. Sick: D. Ar. M. **86.** 370. 1906.
182. B. Moore, W. Alexander, R. E. Kelly, and H. Roaf: A Study of the Pathological Variations in the Acidity of the Gastric Contents, etc. B. J. Vol. i. 1906. Pp. 274-296.
183. F. W. M. Palmer: Variations in the Hydrochloric Acid of the Gastric Contents in Cases of Carcinoma in Man. B. J. Vol. i. 1906. Pp. 398-405.
184. G. J. Baradulin: Some Changes in the Blood in Patients with Carcinoma Ventriculi. W. 1906. Nr. 28.
185. B. Moore and F. P. Wilson: A Clinical Method of Hæmalkalimetry, with Application to Determination of the Reactivity of the Inorganic Salts of the Serum in Malignant Disease and other Conditions. B. J. Vol. i. 1906. Pp. 297-327.
186. Clowes, Frisbie, and Glosser: Studies in Cancer Metabolism. Fifth Annual Report Cancer Lab. New York State Dep. of Health. 1903-1904.
187. V. Hansemann: Die Funktionen der Geschwulstzellen. Zt. f. Krebsforschung. Vol. iv. 1906. P. 565.
188. Wilks: Gu. H. Rep. Vol. iv. 1868.
189. Beebe: The Inorganic Constituents of Tumours. A. J. P. Vol. xii. 1904. P. 167.
190. Beebe and Shaffer: The Pent-Ore Content of Tumours. A. J. P. Vol. xiv. 1905. P. 231.

ADDENDUM LITERATURE.

1. Bashford and Cramer: Unpublished Observations. See note of abstractor in Bi. C., vol. iv., Abstract No. 138, p. 65.

2. Copeman and Hake: Note on Determinations of the Amount of Physiologically Active Hydrochloric Acid in the Stomachs of Normal Mice and of Mice suffering from Cancer experimentally produced. L., November 10, 1906, and unpublished observations.

3. E. F. Bashford: The Problems of Cancer. B. M. J., July 18, 1903.

4. Bashford and Murray: The Zoological Distribution, the Limitations in the Transmissibility, and the Comparative Histological and Cytological Characters of Malignant New Growths. Scientific Reports of the Imperial Cancer Research Fund, No. 1. London, 1904.

5. Ehrlich u. Apolant: Beobach. über maligne Mäusetumoren. B. k. W. Nr. 28. 1905.

6. Clowes and Frisbie: On the Relationship between Rate of Growth, Age, and Potassium and Calcium Content of Mouse Tumour. A. J. P. **14**. 1905. P. 173.

7. Bashford, Murray and Cramer: The Growth of Cancer under Natural and Experimental Conditions. Scientific Reports of the Imperial Cancer Research Fund, No. 2, Part II., London, 1905.

8. Bashford, Murray, u. Cramer: Einige Ergebn. der experimentellen Krebsforschung. B. k. W. 1905. Nr. 46.

9. P. Ehrlich: Experimentelle Karzinomstudien an Mäusen. Zeitsch. f. ärztliche Fortbildung. Vol. iii. 1906. Nr. 7.

10. P. Erhlich: Arbeiten a. d. kgl. Institut. f. exp. Therapie. Heft 1. Jena, 1906.

11. E. F. Bashford: On the Real and Apparent Incidence of Cancer. Epidemiological Soc. of London, January 18, 1907. Lancet, January 26, 1907, p. 227.

CHAPTER VII

PATHOLOGY OF METABOLISM IN THE CHILD

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This section does not pretend to give a complete account of metabolism in so far as it applies to children. A few questions will be discussed in which fundamental differences exist between the metabolism of the adult and the child—differences which have caused the nutrition and metabolism of the child to be regarded to-day as a special subject. The reason for this is twofold.

In the first place, during the early days of life the child's digestive tract is but poorly protected against outside influences. It reacts to nutritional lesions in quite a characteristic manner; its metabolism is profoundly altered by disturbances which at a later age play no part at all, or but a slight one, so that a large area is covered by metabolic and nutritional diseases in infantile pathology.

It cannot be definitely said to what age this special infantile condition —characterized by the facility with which nutritional disturbances arise— may extend.

We often speak of "infant metabolism," but the denotation of the word "infant" is no more definite. Whereas some authors—*e.g.*, Camerer (1)—include under infancy the time from birth to the eruption of the first tooth, others term the period of infancy as that in which only fluid food is consumed, and others, again, limit infancy to the first year of life. None of these limits, however, properly includes the time in which the organism of the child is characterized by unstable metabolic processes. This period undoubtedly includes also the second year; but the development of the natural mechanism for the protection of the digestive apparatus is not completed even within this period, and first attains its maturity in the following year of childhood.

The second circumstance which underlies the special position assigned to infantile nutrition and metabolism is that, in the case of the adult, nourishment only serves to replace the body tissues which have been used up in the maintenance of temperature and the performance of muscular and glandular work. The child requires material to provide for body growth, and also for the storing of potential energy. This very fundamental difference is physiological. Among sick children cases occur in which, for the time being, we only aim at avoiding

loss of body substance. On the other hand, in adults (for instance, in consumptive diseases) nourishment is required not only to maintain the balance of metabolism, but also to assure a return of the body to its normal weight.

I.—THE CHEMICAL COMPOSITION OF THE CHILD'S TISSUES.

In order to determine how far the chemical composition of the child's body is altered by abnormal metabolism, it is necessary to first consider the chemical composition of the newly-born. A comparison of these figures with those obtained from analysis of the bodies of sick children will afford some insight into those metabolic disturbances the final effect of which is manifested by alterations in the chemical composition of the body.

The number of chemical researches made upon the tissues of children has not hitherto been large. Of course, only those of newly-born infants are of any physiological value ; for obvious reasons there are no researches on healthy older children.

In reviewing the literature already collected by Czerny and Keller (2), which includes researches by Giacosa, Michel and Hugounenq and Cornelia de Lange, we shall content ourselves with quoting only the very exact figures of Camerer and Söldner (3), which refer to six newly-born children. The children weighed 2,616 to 3,348 grammes (5·7 to 7·6 pounds), and only differed slightly from one another. Average figures only are quoted.

	Weight.	*Water.*	*Dry Substance.*	*Fat.*	*Ash.*	*Albumin and Mucin.*	*Extractives.*	*Carbon.*	*Hydrogen.*	*Nitrogen.*
Total body in grammes ..	2,821	2,026	795	348	75	330	42	449·6	67·15	55·8
100 grammes of fresh substance	—	71·8	28·2	12·3	2·7	11·7	1·5	15·9	2·38	1·98

100 grammes ash contained : 7·06 K_2O, 7·67 Na_2O, 38·08 CaO, 1·43 MgO, 0·83 Fe_2O_3, 37·66 P_2O_5, 6·61 Cl, 0·11 Al_2O_3, 0·03 Mn_3O_4, 2·02 SO_3, 0·06 SiO_2, 0·53 CO_2.

The figures of Camerer and Söldner not only show little variation in themselves, but are sufficiently in agreement with those previously published by Hugounenq, De Lange, Giacosa, and Michel.

The figures relating to the chemical composition of sick children who have died of digestive disturbances are much less numerous. The entire collection of facts relating to this subject includes only a very few investigations. With the exception of Ohlmüller's (4) old experiments, which relate to the amount of water in the bodies of children suffering from gastro-intestinal disease, only two investigations can properly be considered relevant.

Sommerfeld (5) investigated the water, fat, nitrogen, and total ash content in two children. One of these was four weeks old, and marasmic; the other was well nourished, the cause of death being enteritis and furunculosis. The other series of investigations were carried out at the Breslau clinic upon children aged thirteen days, three, two and a half, and three and three-quarter months respectively (6).

Weights in Grammes.

Author.	*Weight.*	*Water.*	*Dry Substance.*	*Fat (Ether Extract).*	*Ash.*	*Nitrogen.*
Sommerfeld (Case II.)	4,340	3053·0	1287·0	568·9	118·7	98·7
Steinitz (Case I.) ..	1,551	1101·5	449·5	—	44·8	37·7
,, (Case II.) ..	2,625	2098·2	526·8	37·9	86·9	60·9
,, (Case III.) ..	1,960	1612·4	347·6	35·9	62·7	41·7
,, (Case IV.) ..	3,190	2547·8	642·2	63·6	106·7	80·0

Percentages of Fresh Substance.

	Water.	*Dry Substance.*	*Ether Extract.*	*Ash.*	*Nitrogen.*
Sommerfeld (Case II.) ..	70·15	29·85	13·11	2·73	2·27
Steinitz (Case I.) ..	71·00	29·00	—	2·90	2·40
,, (Case II.) ..	79·9	20·10	1·45	2·73	2·32
,, (Case III.) ..	82·3	17·70	1·80	3·20	2·13
,, (Case IV.) ..	79·9	20·10	1·99	3·34	2·51

Percentages of Ash.

Author.	K_2O.	Na_2O.	CaO.	MgO.	Fe_2O_3.	P_2O_5.	*Cl.*
Steinitz (Case I.)	8·30	8·7	37·8	1·1	1·0	39·8	6·5
,, (Case II.) ..	7·20	7·7	38·1	1·2	1·2	38·7	6·1
,, (Case IV.) ..	6·85	7·8	37·8	1·3	—	36·3	5·7

When we examine these figures, it becomes very clear that the factor of predominating import in the relative composition of the infant's tissues—that is to say, the proportion of fat—varies between wide limits. In the newly-born it amounts to 12·3 per cent.; in Sommerfeld's Case II. to 13·11 per cent. On the other hand, in the three marasmic children it only reached 1·45 to 1·99 per cent. It is clear that the value of the other factors would be considerably modified if the fat were eliminated from the calculation.

In this case the following figures appear, which are purposely compared with those of Camerer and Söldner:

Percentages in Fresh Substance freed from Fat.

Author.	*Water.*	*Dry Substance.*	*Ash.*	*Nitrogen.*
Camerer and Söldner	81·9	18·1	3·03	2·26
Sommerfeld (Case II.) ..	81·0	19·0	3·15	2·61
Steinitz (Case II.)	81·1	18·9	3·36	2·35
,, (Case III.)	83·8	16·2	3·26	2·17
,, (Case IV.)	81·5	18·5	3·34	2·56

In all the cases hitherto investigated the gross chemical composition of the children suffering from gastro-intestinal disorders remained the same as that determined by Camerer and Söldner in new-born infants, with the exception of the proportion of fat, which is liable to great variation.

As we know that the composition of healthy new-born infants is not identical with that of the grown man, the latter being poorer in water and richer in ash, the analytical results from new-born children must not be compared with those from sick children of two to four months of age without further remark. But the general variation in composition occurs so slowly in the course of many years that it is certain that no error, or only a slight one, will be incurred by assuming with Camerer that at the age of five months the composition of the child's body is not very different from that of the newly-born.

Under this supposition the relative composition of the body cannot be influenced by digestive disturbances, but remains constant. With the exception of fat, it does not therefore seem possible to rob the organism of any of its functionally important constituents. If a loss occurs of any organic or mineral constituent, we must suppose, which is improbable, that the body, poorer in this constituent, increases as regards the remainder in correspondingly altered proportions; otherwise we must assume that it suffers loss merely through a disappearance of tissues in proportionate ratios, seeing that its composition remains unchanged.

This theory, which has much to support it, may throw some light on the origin of the atrophy, which is alimentary in origin. For it makes it conceivable that a defect in nourishment—*e.g.*, deficiency of chlorides in an entirely cereal diet, or a reduced alkali excretion in a diet over-rich in fat, checks the subsequent growth of the body, or brings about a loss of weight. It must, however, be borne in mind that we are only considering the analysis of the child's body as a whole. It is quite possible that a removal of the soluble organic compounds, or of the mineral components of the organs more important to life, may occur and escape detection owing to compensatory change in the less important organs. In this case the organs important to life might have a different composition in sick children and in the newly-born without its appearing in the analysis of the whole body. A decision can only be arrived at by separate analyses of single organs in children with gastro-intestinal diseases and in the newly-born, as was originally made in the first place by Ohlmüller as regards the water and fat, and later by Sommerfeld as regards muscle.

Recently a series of researches has been added to the figures quoted above, concerning the chemical composition of a child which succumbed to an exclusively cereal diet at the age of four months [Steinitz and Weigert (69)]. The data of present interest, which we may compare with the previously quoted Case IV. of Steinitz, are as shown on the following page.

These differ from all figures previously quoted; the proportion of water and the content of alkali and chlorine in the child fed on cereals are notably diminished.

Percentages of Fresh Substance Free from Fat.

Author.	*Water.*	*Dry Substance.*	*Ash.*	*Nitrogen.*
Steinitz (Case IV.)	81·50	18·50	3·34	2·56
Cereal-fed child	77·75	22·25	3·94	2·97

Percentages in—

Author.	*Fat-free Dry Substance.*			*Ash.*		
	K_2O.	Na_2O.	Cl.	K_2O.	Na_2O.	Cl.
Steinitz (Case IV.) ..	1·2360	1·434	1·0370	6·85	7·80	5·7
Cereal-fed child	0·8953	0·933	0·4952	5·06	5·28	2·8

But in the case of this child we have to do with circumstances utterly different from the chronic nutritional disturbances to which the other children succumbed, so that the values found for its chemical composition do not negative the theory advanced as to the constancy of the chemical composition of infants. The cereally fed child suffered from acute diarrhœa, which in the last days of its life had produced a reduction of nearly a quarter of its total body-weight. There is therefore no doubt that this loss of body-weight was in great part made up of water and alkalies. The analysis has in consequence given results which differ from those of the other children, because death occurred so rapidly that no equalization of the composition of the body was possible, such as would doubtless have taken place in a short time longer.

II.—PROCESSES IN THE GASTRO-INTESTINAL CANAL.

A.—GENERAL REMARKS ON FOOD.

Since the function of the alimentary tract in the young child differs quantitatively from that of the adult, it is clear that a child's food must be of a different quality from that of an adult. The fact that the child is practically always born without teeth, and that six to ten months elapse before the eruption of the first tooth, makes a fluid diet a necessity. This consists of the mother's milk, the milk of various animals (cow, goat, and ass), and also vegetable decoctions in more or less complicated form.

The use of human milk is limited to infants. The only experiment designed to establish its value for adults (7), which was not altogether planned on satisfactory lines, seems, indeed, to show that it is not nearly so well digested and absorbed by adults as by infants. The milk of

animals, more especially cow's milk, plays a very important part in the nourishment of adults also. Temporarily, it may even form the sole article of diet, but its use is restricted within somewhat narrow limits, as it does not contain sufficient quantities of certain cell substances necessary to adult life. Thus its iron content (as also with human milk) is so small that the necessary amount of iron for the organism cannot be supplied by it alone, and we must assume that a store of iron is present in the newly-born. Such a store has been proved by Bunge (8) for certain rapidly-growing animals; it appears also to be present in infants—at least, Philippson (9) has found a higher content of organic iron in the isolated liver cells of the newly-born than in those of children at the end of the first year. But since this store of iron is used up in the course of the first month of life, the exclusively milk diet should be discontinued at any rate soon after the eruption of the teeth, or supplemented by a mixed diet, and especially by vegetables rich in iron.

B.—SECRETION OF SALIVA.

Since the child under normal conditions takes during the first months a fluid diet which neither needs insalivation nor contains starch, we may expect *a priori* that the secretion of saliva in the newly-born should be either not present or only incompletely developed.

The earlier authors who investigated this question (10) showed that the secretion of saliva during the first days of life was but slight, and that the collected saliva contained no diastatic ferment. This assumption was, however, refuted by later observers. Schiffer (11), Korowin (12), Zweifel (13), Schlossmann (14), and Schilling (15) always found ptyalin in the saliva of infants, whether sick or healthy, whether newly-born or a few weeks old.

As regards the place of origin of the sugar-producing ferment, Zweifel, by examining the watery extracts of the glands, found that only the parotid, and not the submaxillary gland, produced ptyalin in the newly-born. Schilling found the ferment also in the secretion of the submaxillary gland.

C.—PROCESSES IN THE STOMACH.

1. Hydrochloric Acid and Pepsin.

Epstein's method has facilitated the investigations of the secretory functions of the stomach of the child. The greater number of observers do not, however, sufficiently distinguish between healthy and sick children. This drawback is not an important one; the difference in the secretory function of the healthy and sick stomach is one of degree, and not of kind.

That HCl constitutes one of the normal products of the secretion of the stomach is established beyond all doubt. On the other hand, the question propounded by many authors as to whether lactic acid is a constituent of normal gastric juice in infants is not yet solved. De Jager (17)

and the two Labbés (18) assert that the acidity of the gastric juice in infants depends upon organic acids, especially lactic acid. Sotow (19) denies its presence in healthy breast-fed children. Escherich (20) and Troitzky (21) consider it a normal product. Moncorvo (22), Bauer, and E. Deutsch (23) describe the production of lactic acid as a normal phenomenon at the beginning of gastric digestion. On the other hand, Cassel (24) and Thiercelin (25) regard the appearance of lactic acid as a pathological symptom. All these authors have been content with Uffelmann's reagent or a titration of the ethereal extract. A recent investigation is reported by Sedgwick (186). He has found in the stomach contents of both healthy and sick infants a ferment (lipase) which decomposes the milk-fats in food into free, higher fatty acids. The action of this ferment explains the relatively high acidity in the infant's stomach.

Hydrochloric acid was isolated by Wohlmann (26) from the gastric contents of healthy children immediately after a meal, but it was first recognised as free acid a quarter to two hours later, as it was concealed by combination with the albumin and the alkaline salts of milk. Other workers confirmed this (23, 27, 28, 29). The amount of free acid then increases, and reaches its maximum in about two and a half hours. In artificially fed children the period which elapses before the appearance of free acid is longer, as cow's milk and its compounds generally contain more bodies which combine with the acid.

The view of certain authors [Thiercelin (25), Clopatt (30), Einhorn (31)] that free HCl does not exist under normal conditions in the infant's stomach is due to the fact that they investigated sick children only. It is certain that the secretion of HCl, which normally is smaller than in adults, is often entirely suppressed by even slight disturbances of digestion.

Wohlmann (26) found in the case of premature and dyspeptic breast-fed children a gradual rise in the acidity of the gastric juice, a lower proportion of acid, and a delay in the appearance of free HCl.

Heubner (32), who examined the filtered gastric juice, found free HCl twelve times in forty-six sick infants. In the remainder he showed that the proportion of combined HCl corresponded to the period of digestion.

Bauer and Deutsch (23) found the combined acid reduced in children suffering from gastro-intestinal disease ; von Hecker (33) and Cohn (29) failed to find free acid.

Cassel (24) and Wolf and Friedjung (34) found free HCl in only a part of the cases investigated. They are not inclined to ascribe a pathological significance to changes in the chemical functions of the stomach.

Finally, in this connection Meyer (35) takes an extreme standpoint. He observed in certain cases of cholera infantum a diminution or absence of acidity, but thought that the secretion of gastric juice was not influenced by nutritional disturbances, and held that the investigation of the chemical functions of the stomach was of quite secondary importance.

Cohn (29), after investigating a great number of infants with gastro-intestinal diseases, could not prove the existence of hyperchlorhydria. On the other hand, certain records indicate that hyperchlorhydria is not improbably present in a lesion fairly often described—namely, congenital hypertrophic stenosis of the pylorus.

A case described by Leo (28) is, strictly speaking, not applicable here, as hyperchlorhydria was not proved, but only inferred from a positive result with Günzburg's test and a very high total acidity. The same objection applies to the eight cases published by Oddo and De Luna (36).

Knöpfelmacher (37) reported a case of definitely determined hyperchlorhydria (titration with dimethylamidoazobenzol as indicator, Toepfer's method). Knöpfelmacher considered that the hyperchlorhydria was primary, and the stenosis of the pylorus secondary to the irritation. Meyer (35) and Freund have, moreover, published similar cases, but fail to give quantitative estimations of the HCl.

The well-known property which milk possesses of entering into chemical composition with HCl has a special significance in the physiology and pathology of gastric digestion. This property of milk was first described by Leo (28). Escherich (39), when investigating the essential differences between human milk and cow's milk, found that 50 c.c. of human milk combined with 8 to 9 c.c., and 50 c.c. of cow's milk combined with 15 to 16 c.c. of one-fourth normal acid solution. Müller (40) confirmed this observation, and widened its scope by establishing the fact that 42 per cent. of milk-salts and 58 per cent. of albumin were necessary for combination with the HCl. The property of milk of combining with HCl plays a double part in pathology. In the first place, it influences the bactericidal power of the HCl. Hamburger has shown that the combined HCl has practically no antiseptic power (41). On the other hand, free HCl, in the concentration met with in the stomach—while not actually bactericidal—has at least an inhibitory action on the growth of organisms.

Hamburger's test-tube experiments are confirmed by Langermann's (42) observation on the influence of HCl on the flora of the infantile stomach. In Langermann's cases the number of organisms was not dependent on the number of organisms in the food, but on the amount of free HCl in the stomach contents. When volatile fatty acids were employed the bacterial content was high, free HCl being absent. The artificial addition of HCl, however, acted as an antiseptic.

As the power of human milk for combining with HCl is less than that of undiluted cow's milk, so the antiseptic power of the stomach contents of the naturally fed child is greater than that of the artificially fed. Moreover, the system of three to four hourly pauses between meals, especially advocated by Czerny (43), is supported by this fact. For since, in the case of healthy, naturally-fed children, free HCl appears in the gastric contents at the earliest in one and a quarter hours, and in the case of artificially-fed children first in two hours, a thorough disinfection cannot be attained without allowing a considerable interval. If this is not inserted between two meals, the stomach has no time to disinfect its contents, and the way is thrown open to all possible bacterial invasions. Besides, Czerny and Wachsmuth (44) have also drawn attention to this defect, and have attempted to explain by its means the higher mortality of artificially fed children.

The high combining power of cow's milk with HCl must, on the contrary, exert a good influence in the cases to which allusion has been

made above of probable hyperchlorhydria, for here a desirable combination occurs with the HCl which has been either primarily or secondarily secreted in excess. These are the very few cases in which feeding with undiluted cow's milk is to be preferred to natural feeding. In this connection the case of Knöpfelmacher (37) may be referred to. A similar case of Freund's (38), in which a congenital stenosis of the pylorus was permanently cured by the administration of undiluted curdled milk, may also be cited. The secretion of pepsin is not influenced by digestive disturbances to the same extent. At least, nearly all authors who have given attention to the proteolytic enzyme of the stomach report its presence in the gastric juice of children suffering from gastro-intestinal disorders. Only a few authors—as, for instance, Thiercelin (25) and Leo (28)—mention some cases of hypopepsia or deficiency in pepsin.

Toch (45) found pepsin and peptone not only in the gastric contents of healthy infants, but even in those who were seriously ill. But it is questionable, according to his experiments, whether the latter was a product of peptic digestion ; for the gastric juice which he obtained did not peptonize fibrin till 0·3 per cent. HCl was added. As the production of peptone in the stomach by bacterial action has not been proved, its presence may perhaps be explained by assuming that the coagulation of caseinogen sets free a peptone-like body. This point will be further considered in dealing with the action of rennet.

2. Rennet Fermentation.

All authors who have dealt with the presence of the rennet enzyme in the stomach of children suffering from gastro-intestinal disorders [Szydlowski, Cassel, Meyer, and others] are agreed that it is invariably to be found. Szydlowski (46), who has made the fullest investigations, described it as constant ; its activity was independent of the nutrition, age, health, or development of the child, as also of the reaction of the gastric juice. He could not find in infants any precursor of the rennet ferment.

Certain differences exist in the form of clot produced by rennet from cow's milk and human milk in the stomach, and as regards digestibility these differences are of great importance.

Rennet enzyme is added to fresh undiluted cow's milk ; this, in a short time, will coagulate into a gelatinous, coherent clot, whereas human milk, under the same circumstances, usually does not coagulate. It is only on the addition of traces of HCl that a slow, incomplete, and finely flocculent coagulation occurs.

This obvious difference was formerly held to explain the indigestibility of cow's milk [Küffner, Vogel, Biedert, and others], and many endeavours were made by pædiatrists to make the coagulation of cow's milk in the stomach similar to that of human milk. Scientifically, all these views are insufficiently supported. Cow's milk only coagulates with a firm clot when it is undiluted, fresh and absolutely still. When it is moved, a fine flocculent deposit of casein always occurs [Szydlowski].

In the stomach cow's milk coagulates in fine flakes just like human

milk, if its proportion of fat is so raised that it bears the same ratio to the protein as it does in human milk [Biedert]. The same thing occurs if albumin [Schlossmann], or a gelatinous or cereal decoction is added to the cow's milk.

On the other hand, an excessive amount of fat has been shown to influence protein digestion unfavourably. Bell (207), as the result of his observations on children fed with milk over-rich in fat, concludes that the amount and digestive power of the gastric juice is diminished, and thinks that the interference with protein digestion may be partly mechanical, the food particles being coated with a fatty envelope, or the mucous membrane of the stomach clogged up by the same agent. He alludes to Labapoff's experiments, described in Pawlow's "Work of the Digestive Glands," showing that after 400 grammes of flesh had been given, the average of 13 c.c. of gastric juice was secreted during each of the first four hours, having a digestive power of 4·47 millimetres. The same amount of flesh taken one and a half hours after 75 c.c. of olive oil only gave rise to an average of 4·5 c.c. of juice, with a digestive power of 2·69 millimetres.

We need only expect, therefore, a heavy lumpy clot of casein in the infant's stomach, when not only milk is given fresh and undiluted, but when, in addition, the motor power of the stomach is unusually weakened.

How far the large clot then formed is bad for the infant is at present not understood.

It is, indeed, generally held that the large milk-clot offers great resistance to the peptonizing process, but this view rests merely on supposition, and certain researches of Escherich's (47) negative this point of view.

	Milk in Each Test.	*Grammes Nitrogen.*	*Amount of Nitrogen in Peptone from Artificial Gastric Digestion.*			
			Heavy Clot.		Fine Clot.	
			Not Shaken.	Shaken.	Not Shaken.	Shaken.
Experiment I. ..	100 c.c.	0·504	0·1415 (28 per cent.)	0·1415 (28 per cent.)	0·1404 (27·8 per cent.)	0·1296 (25·7 per cent.)
Experiment II...	100 c.c.	0·4516	0·1594	(35·3 per cent.)	0·1756	(39 per cent.)

As the table shows, the artificial gastric digestion of the casein clot occurs equally well whether the clot is massive or flocculent.

While in the views of older authors prominence was given to the idea that rennet exercised a retarding, if not a preventive, influence on the digestion of milk, in recent times the fact has not been lost sight of that the rennet ferment is of importance in the digestion of albumin. These views tend in two directions.

Some authors [Danilewski, Okouneff (48), and Sawjalow (49)] ascribe an important part to rennet in the conversion of peptone into albumin (albuminization). This occurs in the stomach and small intestine—that is, in the mucous membrane of the alimentary canal—and consists in a dehydration of peptone. Its object is to change the various products

of digestion, which are brought about by feeding on various proteins, into a homogeneous substance—"plastein"—which serves for the formation of tissue substance.

Rotondi (50) has recently pointed out another way in which rennet influences digestion. Hammarsten (51) had formerly supported the view that caseinogen was split by the rennet ferment into an insoluble body—casein (paracasein)—and into the soluble whey protein. Rotondi now shows that after precipitating the casein with acetic acid, and again heating, more nitrogen remains in the filtrate if the milk has been previously treated with a small quantity of rennet. He therefore concludes that by the digestive action of the rennet ferment on the casein a protein body is split off, soluble in acetic acid, and not precipitated by heat. When these observations on the digestive actions of the rennet enzyme are confirmed, they will be of importance for the theoretical comprehension of milk digestion. The interest, as far as the pathology of metabolism is concerned, is limited. For, just as is the case with the other gastric enzymes, the rennet, under all circumstances, even in exceedingly sick children, is present and active in all phases of digestion. Therefore the newly inaugurated attempt to increase the digestibility of milk by the addition of rennet (52), and also the good results obtained by this method, must be accepted with reserve.

D.—PROCESSES IN THE INTESTINE.

Whereas in the removal of the stomach contents we have a means of directly ascertaining the processes of gastric digestion, in the study of intestinal processes we are limited to analysis of the fæces and urine, or to post-mortem researches on the secretory function of the intestine and its tributary glands. For this reason there are still many gaps in our knowledge of the pathological processes of the intestine.

As regards the functions of the liver, A. Koeller's (53) researches on its urea-forming power in sick children will be discussed in the section on ammonia excretion by the kidneys. The detoxicating function of the liver has been studied both in sick and in healthy infants. As to the composition of bile in children (especially the contents of the gall-bladder), the analyses by Jacubowitsch (53A) and Baginsky and Sommerfeld (53B) are available. On the other hand, the question as to whether disturbances in the secretion of bile occur in infants has not yet been experimentally determined. The almost white stools, so often noted in children suffering from gastro-intestinal disorders consequent on overfeeding with milk—which almost resemble the stools in acholia—cannot be regarded as an indication of diminished biliary secretion. These stools probably owe their appearance to some cleavage in the bile pigments which first occurs in the intestine, a fact which will be further considered when we deal with the reduction processes which occur in the gut.

The pancreas has for a long time been an object of interest to the pædiatrist, and especially the question as to whether a diastatic enzyme

is present and active in the pancreas from birth. This question has also a practical significance, for upon it depends our decision as to whether or not a newly-born or quite young child can assimilate starch in its diet—in other words, whether it is able to invert sugar.

In the older literature [Korowin, Zweifel] the diastatic power of the pancreas in the newly-born and in children during the first weeks of life was totally denied.

Moro (54) recognised traces of a diastatic enzyme in the newly-born by making a thorough extraction of the pancreas. He found large amounts of diastatic enzyme in the stools and intestinal contents of suckling infants. These, however, originated in part from the pancreas, and in part from the intestinal glands and the mother's milk.

Kerley, Mason, and Craig (208), by an examination of the stools of sixty infants fed exclusively on starch, did not observe any evidence of starch in thirty-three cases, and in twenty it was only occasionally present. Dextrin was present in more than half the cases. They also isolated a reducing ferment from the fæces of twenty-six breast-fed infants under two months old. One grain of fæces (0·064 gramme) was able to convert $\frac{1}{20}$ grain (0·0032 gramme) starch. This result was also obtained when the fæcal extract was passed through a Berkefeldt filter, showing that it was not a direct bacterial action, and also when made from meconium, showing that it was not due to ferments in the milk. On the other hand, Gillet (55), as a result of post-mortem researches, states that in the first months of life the sugar-forming enzyme is not present in the pancreas. Under pathological conditions the zymogenic activity of the pancreas appears to be disturbed in various ways. According to Gillet, the pancreatic juice loses its peptonizing and diastatic power in conditions of intestinal catarrh. Jacubowitsch (56), however, has shown that the sugar-forming enzyme is but little delayed by illnesses, and that, concomitantly, the peptonizing ferment is much more markedly affected; in hereditary syphilis and cholera infantum, among others, the enzyme cannot be detected. In the same way, according to this author, the fat-splitting enzyme of the pancreas is considerably diminished in many very different pathological conditions.

The investigation of the refuse of the food, the fæces, plays a greater part in our knowledge of the processes in the intestine. For it enables us to discover at once the degree of absorption of the ingested food, and what portions of it cannot be utilized. Moreover, it permits of very wide conclusions being drawn as to the activity of the glands of the intestine and the organs attached to it, and enables us to decide whether we have to deal with a normal or pathological secretion.

General Characters.—The fæces of a breast-fed infant are distinguished by their golden yellow colour and their soft, homogeneous consistency. The normal stool, however, has not these characters under all conditions. The appearance of the stools of breast-fed children varies within considerable limits according to the proportion of fat in the milk; only when the child is fed on milk rich in fat is the "classical"[1] pultaceous stool obtained [Gregor (57)]. In the periods in which the secretion of

[1] In medical literature, this really involves a gross misuse of the word.

the mammary glands is poorer in fat the stools are more copious, more watery, unequally coloured, and contain whitish or yellowish stained flakes, which are embedded in a more or less green-coloured mucus.

It has been urged against Gregor's researches by P. Reyher (57A) and S. Engel (57B) that his estimations of the fat contained in human milk leave something to be desired in point of accuracy. But the fact that the appearance of the fæces depends on the varied composition of the human milk is not affected by this objection.

The smell of the fæces in breast-fed children is acrid, but not fœtid. Their reaction to lacmus is acid, owing to the production of lactic acid. On exposure to the air the yellow colour becomes green owing to the oxidation of bilirubin into biliverdin.

The colour of normal fæces from children fed on cow's milk is also yellow, but not so bright a yellow as the fæces of the breast-fed child; on standing exposed to the air, they turn mostly white or greyish-yellow. If carbohydrates replace the cow's milk as food, the yellow colour of the stools is more intense.

The fæces of the artificially fed child are strong-smelling, owing to decomposition products, even in the absence of any symptoms of illness. The presence of these products, which depends on reduction processes occurring in the intestine, also accounts for the stools being mostly alkaline to lacmus. On the addition of carbohydrates to the diet of cow's milk, the reaction of the fæces shows an acid phase, and the smell of decomposition disappears. The difference in the nature of the intestinal processes in the case of naturally and artificially fed children is expressed in the acidity of the stools.

According to Blauberg (58), 100 grammes of human milk are neutralized by 25 c.c. normal soda solution, and 100 grammes of cow's milk by 11·33 c.c.

Hellström (59) found the acidity of the stools in breast-fed children equal to 2·6 c.c. normal soda solution, Langstein (60) to 2·1 to 3·7 c.c.

Hedenius has published researches on the acidity of the stools with a diet of various carbohydrates. He showed that the acidity (according to Blauberg) is liable to considerable variation; it is higher in younger children, who digest carbohydrate badly, lower or nil when the carbohydrate in the intestine escapes decomposition.

The content of the fæces in albumin, fat, and carbohydrate will be further dealt with below under the heading of Absorption.

Experiments on the processes of decomposition and fermentation of the fæces in the intestine show that these processes, which are both produced by the action of bacteria on the food and intestinal juices, are so nearly related that it is best to deal with them together.

Various causes contribute to the fact that, normally, in the intestines of infants no putrefactive processes occur. According to Senator (62), putrefaction is prevented by the rapid passage of the food through the gut. This being the case, the fæces, if left to themselves, should putrefy outside the body. As a matter of fact, this does happen. At any rate, Winternitz (63) and Blauberg (58) recognised the presence of indol, phenol, skatol, and oxy-acids, the former observer in the milk-stools of

dogs, and the latter in the stools of breast-fed and bottle-fed infants, after long keeping in a thermostat.

The fact established by Hirschler (64), Rovighi (65), Schmitz (66), Eisenstadt (67), and others, that milk is usually incapable of putrefaction, and that the employment of milk or its products (cheese, kephyr) arrests or diminishes intestinal putrefaction, accounts for its absence in milk diet.

According to Hirschler, Winternitz, and Schmitz, carbohydrates prevent the putrefactive decomposition of casein.

We must imagine that, normally, in the intestine the casein is protected from putrefaction by the preponderating influence of fermentation. According to Escherich (69), as a rule, only two sorts of bacteria are present in the intestine—the *Bacterium lactis aerogenes* and the *Bacillus coli communis ;* the first in the small, the second in the large intestine.

E. Moro (72) found in the small intestine the *B. coli* and *lactis aerogenes* preponderating over *B. bifidus* from the cæcum upwards. All three are markedly fermentative, but they have no proteolytic or peptonizing action. The acid reaction produced by fermentation in the intestinal contents prevents putrefaction.

It is different under pathological conditions. Here we have not only to reckon with the intestinal contents, mainly consisting of milk or the products of its digestion, but at the same time with an increased secretion of intestinal mucus, and this is extraordinarily liable to putrefaction. There is no doubt that the stinking evacuations of infants suffering from gastro-intestinal diseases—when it is shown by the composition of the fæces that there is no possibility of decomposition of the food—owe their character solely to the putrefaction of the intestinal secretion.

From another point of view Biedert (70, 71) and Baginsky (73), in opposition to the fact established by all other authors, that food cannot ferment in the infant's intestine, indict the protein given in artificial food as responsible for the origin of gastro-intestinal disturbances. The former falls back upon the deficient absorption of the casein of cow's milk, which, as will be seen later, does not really occur. Through this are produced in the intestine " deleterious food residues," and these, again, give rise to putrefaction and the presence of toxic products.

Baginsky ascribes to the saprophytic bacteria, when they are not overpowered by the organisms of fermentation, the power of producing from the protein of the food toxic bodies resembling peptone, ptomaines, indol, phenol, and especially ammonia. All these toxic products of the putrefaction of albumin on entering the lymph and blood stream give rise to the severe symptoms of cholera infantum.

It cannot be denied that the putrefactive process which both these authors consider so important in the pathogenesis of gastric disturbances is, as a matter of fact, of no little significance in the symptomatology of the gastro-intestinal disorders of infants ; this is certainly, however, no primary event, but can be explained on the grounds of a pathologically increased intestinal secretion. Moreover, from this point of view artificially fed children are worse off than those nourished naturally. For in every case of artificial feeding there is already an increased intestinal

secretion, which is further shown by the fact that in normal breast-fed children no excretion of indican is noted in the urine [Senator, Hochsinger, Zamfiresco], whereas some is usually found in the case of artificially fed children.

Momidlowski (74) found that in children suffering from gastro-intestinal diseases the indicanuria was more intense in proportion to the severity of the intestinal affection which gave rise to the putrefactive process.

According to Kast (75), Stadelmann (76), Biernacki (77), Mester (78), Schmitz (79), and Wasbutzki (80), moreover, the secretion of HCl in the stomach has considerable influence on putrefactive processes in the gut; and considering that, as we have shown in a preceding section, the majority of the gastro-intestinal disturbances in infants are accompanied by a diminution in HCl production, this must give an additional impulse to the putrefaction of the intestinal secretions.

Whereas putrefactive processes occur in the intestine with an alkaline reaction, and accompanied by a decomposition of protein or protein-like material, fermentation in the intestine takes place with an acid reaction, and accompanied by breaking up of carbohydrates. The only material for fermentation in naturally fed children is milk-sugar, but in artificial diets other sorts of sugar, such as saccharose and maltose, occur, and cereals containing starch and dextrin. According to Escherich (69), the fermentation products are lactic acid, carbonic acid, and hydrogen. Other authors [Baginsky, Emmerling] consider lactic acid only a secondary product of fermentation, as they have found acetic and especially succinic acid to be the principal fermentation products of milk-sugar.

The physiological significance of fermentation lies in the fact, already pointed out, that through acid formation the intestinal flora is influenced, and putrefaction is thus prevented or diminished. Moreover, as Schmidt (81) has recently remarked, the products of fermentation serve to stimulate peristalsis, and thus, by preventing the ingesta remaining too long in the intestine, to hinder intestinal putrefaction. Slight degrees of fermentation are needful to maintain the physiological processes in the intestinal tract of infants.

On the other hand, should any etiological factor (such as overfeeding or too short intervals between meals in the breast-fed children, and excess of starchy food in the artificially fed) produce abnormal fermentation, it will also give rise to irritation of the wall of the gut, as Widerhofer (82), Escherich (83), and recently Raczynski (84), have shown, and thus cause increased secretion, desquamation, and peristalsis. This so-called fermentative dyspepsia is marked by the formation of gas (especially hydrogen), and by the occurrence of numerous stools of a frothy and acid character.

Raczynski, who has recently described this symptom-complex in breast-fed children, considers as *causa causans* an excess of fatty acids occurring as a result of the preponderance of fermentative bacteria in the intestine, and causing a defective fat absorption. For example, he cites the analysis of the fæces in the case of two children, both nursed by the

same wet-nurse. One was normal, the other dyspeptic. The following observation illustrates the point in question :

	In 100 Grammes Dry Fæces.	
	(*a*) Dyspeptic Child.	(*b*) Normal Child.
Free volatile fatty acids	7·31	0·790
Free fixed fatty acids	1·87	0·749
Saponified fatty acids	10·77	3·117

The opposite condition in which fermentation of carbohydrates and putrefaction of protein coexist is of much more interest from the therapeutic standpoint. Empirically, when the stools are foul it is always found that protein food has been limited, and the deficiency made up with carbohydrate. Escherich (85), however, was the first to exactly explain the position, and to introduce an important factor in the treatment of gastro-intestinal diseases by absolutely checking the bacterial growth of the intestine, and ending the peculiar kind of decomposition to which it gives rise.

Schmidt (81), considers that he has found an important diagnostic index of the amount of fermentation in the intestine in the fermentation test which he has introduced. This consists of allowing the freshly-passed fæces diluted with water to undergo fermentation in an incubator. The amount of gas formed in twenty-four hours (early fermentation) is measured ; the quantity acts as an index of the extent of fermentable carbohydrate in the fæces.

Pusch (86) could not find any early fermentation in healthy breast-fed children. Its appearance in the fæces of breast-fed children he considered as a sign of disturbed carbohydrate digestion. In sick and " irrationally " fed children it was almost always demonstrable.

Callomon (87), who repeated the researches of Pusch, was unable to confirm them. Both he, and later Langstein (60), observed early fermentation in normal breast-fed children ; for the rest, the amount of fermentation on a diet of soluble carbohydrate and cereals varied so much in the same child that its value as a clinical diagnostic sign of the functional activity of the intestine was not by any means apparent. In close relationship with fermentation and putrefaction stand the processes of oxidation and reduction in the intestine ; little, however, is known of their significance as regards the metabolism of infants.

The golden-yellow colour of the infant's stool is due to the presence of unchanged bilirubin. If the stools remain exposed to the air biliverdin is formed, and their colour becomes green.

This oxidation of bilirubin can also take place in the intestinal canal. Then it produces the phenomenon of green stools, to which the older authors attached great importance as a symptom of dyspepsia.

Although it was formerly assumed that the formation of biliverdin took place by the action of acid products in the gut, Pfeiffer (88) stated

that it depended on the action of alkalis on bilirubin. At any rate, he was able to turn the yellow fæces of a breast-fed child green by the addition of dilute potash, or soda solution, or the alkaline carbonates *in vitro*. On that account he supposed that in the gut, whenever for any cause there was an excessive alkalinity, the intestinal contents became green in colour, and that this green colour remained permanent even when in the lower portion of the gut the reaction once more became acid. Whether the events observed by Pfeiffer *in vitro* can also be applied to the processes inside the gut is at present not proved; for the rest, his assumption of an overwhelming degree of alkalinity in the gut (a flooding of the upper part of the intestine with alkaline milk not neutralized by the gastric HCl) is decidedly problematical.

Wernstedt (88B) advances a more plausible explanation of the occurrence of green stools. He attributes the formation of biliverdin to the action of an oxidizing ferment. This ferment he has identified in the intestinal mucus, and more particularly in the leucocytes. Green-coloured stools contain invariably a larger or smaller amount of mucus, and Wernstedt therefore considers that the pathological secretion of mucus is the primary event, and that the oxidation of the bilirubin is secondary.

Our position as to the reduction changes in the bile pigments is better defined than that concerning the oxidizing changes of bilirubin. Schmidt's corrosive sublimate test for fæces provides a simple and certain method of distinguishing between bilirubin and hydrobilirubin. If the fæces are treated with a saturated solution of $HgCl_2$, all specimens containing hydrobilirubin will become red, while bilirubin is converted into green biliverdin. The formation of hydrobilirubin in the intestine occurs with absolute certainty as an accompaniment of putrefactive processes. Bilirubin cannot be demonstrated in the normal stools of adults, and hydrobilirubin hardly ever in the normal stools of breast-fed infants, because in these no putrefaction takes place. On the other hand, as Schikora (90) has shown, the stools of artificially-fed children suffering from no gastro-intestinal disease contain a preponderance of hydrobilirubin.

In frequently passed diarrhœic stools Schikora found the hydrobilirubin diminished, whereas he found it in excess of the urobilin in foul stools evacuated at longer intervals. In the first case putrefaction was hindered by the rapid passage through the gut; in the latter case it was favoured.

Langstein (91) has recently remarked on a still more extensive reduction of bile pigments in the gut. Starting from the observation that infants which were overfed — but undernourished — with cow's milk generally passed white stools similar to those of acholia, Langstein endeavoured to show that in these children, as a matter of fact, a disturbance of the cholipoietic function of the liver does occur, or there is some change in the bile pigments. With this object he used the reagent introduced by Ehrlich (dimethylamido-azobenzaldehyde), which, as Neubauer (92) has shown, reacts with urobilinogen, producing a red colour when heated in an acid solution. Langstein obtained a particularly intense Erhlich's reaction. Thus it is most probable that the urobilinogens are reduction products of hydrobilirubin, and form colour-

less compounds in an alkaline solution ; and so the fact was established that the white stools are not acholic, but that it is a case of an abnormal reduction, whereby the bilirubin is converted into a colourless urobilinogen instead of into urobilin.

As to the gaseous products of fermentation and putrefaction, but few figures are available. Quest (93) has analyzed the intestinal gases in infants. He found that these depended to a great extent on the food, in so far that, by raising the proportion of carbohydrate in the diet, he could also increase the hydrogen in the intestinal gases, and correspondingly decrease the nitrogen. Occasionally marsh gas was found ; the quantitative estimation of H_2S was prevented by the high coefficient of absorption of this gas. The question of the origin of tympanites in infants was not cleared up by the nature of the composition of the gastric and intestinal gases. For this reason Quest assumed as a cause of tympanites, in addition to the intensity of the gas formation, a disturbance of the circulation in the abdominal organs, which prevented a proper absorption of gas.

E.—GASTRO-INTESTINAL TOXINES—DETOXICATION.

The question of the formation of poisons in the intestinal tract, which has recently obtained considerable importance for adults, and has given rise to a class of diseases termed autointoxications, has been but little studied in infants. Czerny (19) was the first to investigate this subject. He put to himself the question whether the diet of infants—that is, either human milk or cow's milk — could serve as material for the production of intestinal toxines. To throw light on this matter, he endeavoured to ascertain whether, from human or cow's milk, he could obtain, either by digestion or under the influence of the bacteria present in the infant's intestine, substances which could be shown to be toxic by animal experiments. As these investigations had a negative result, he then sought for some toxic substance in the fæces. Failure in this search led to the conclusion that the formation of acids in the intestine was the only factor of etiological importance in the alimentary diseases of infants.

Lesage (96) filtered the stools of infants with acute gastro-enteritis through a porcelain filter, and found the filtrate was not toxic for guinea-pigs. In the same way Salge (97) was unable to isolate any substance toxic for animals, either from the stools of children with acute toxic intestinal catarrh, or from the acidophil bacilli, to which he attached considerable importance in the etiology of this disease.

On the other hand, Köppen (98) found a substance poisonous to rabbits and cats when cheese was inoculated with infant's fæces and allowed to stand a long time. This result is no more conclusive for our question than the more significant observation of Finkelstein (99), who found that young goats, whose milk had for one single occasion been mixed with 5 c.c. of fluid fæces from a marasmic infant, became very cachectic and succumbed, although animals fed with fæces of healthy infants remained in good condition.

The only author who found a poisonous body in the fæces of infants is Spillmann (100). With alcoholic and watery extracts of the stools of children with gastro-enteritis he obtained toxic symptoms in animals, and, indeed, in one case was able to produce rickety bone changes in a rabbit by the injection of an extract of the fæces of a rachitic child.[1]

It is thus evident that the attempt to find toxic substances in the fæces of sucklings has failed, and that the explanation of gastro-intestinal diseases as autointoxications from the gut has, up to now, led to no results. These negative results, as will be explained later, caused a number of workers to regard the intermediate products of metabolism as the main factors in the causation of digestive disturbances.

Although we cannot as yet definitely recognise the formation of poisons within the intestine, we know that the gastro-intestinal tract, and the organs attached to it, have certain toxic powers. In infants this power has been ascertained to exist, in the cases of the gastric juice and the pancreas, by means of experiments concerning poisoning by the diphtheria toxine. In both these series of experiments the diphtheria toxine was chosen, not because it plays any part in the gastro-intestinal tract, but merely as an indicator, because the dosage can be exactly regulated, and its action permits of very careful study.

Schutz (102) examined the gastric juice of new-born children—both healthy and suffering from gastro-intestinal disease—as to its action against diphtheria toxine, and found that not only newly-born children, but also those who were sick, secreted a gastric juice which neutralized the toxine. But this function was not constant, and in some cases was absent for no apparent reason.

Von Zaremba (103), who conducted similar experiments with extract of pancreas, proved its capability of combining with toxines in children the subjects of gastro-intestinal disease. He therefore concluded that this power must also be present in healthy children.

The significance of these results must be regarded as all the more important since Behring's (104) recent experiments. Behring's attempt to combat tuberculosis is founded upon the power of the new-born animal to absorb antitoxic substances (antibodies) unchanged from the gastro-intestinal canal; he relies especially on the experiments of Röwer (105), who found that it was possible to saturate newly-born animals (horses and rabbits) with antitoxic bodies from the intestinal canal, whereas this was quite impracticable in older animals. Salge (209) was able to show that, whereas in children antitoxic substances were transmitted by the mother's milk unchanged into the tissues, the milk of other animals did not produce the same results.

Ganghofner and Lange (105A) were able to show that white of egg passed directly from the intestine into the blood-stream of human infants during the first few days of life. Uffenheimer (103B) has, however, questioned the value of the experiments. This author has, moreover, shown

[1] The experiments of Durante (101), who found the watery and alcoholic extracts of the stools of children with gastro-enteritis toxic for guinea-pigs, are not applicable, as the children he observed were in every case at the end of the first or beginning of the second year. One child was only eight months old at the beginning of the experiment, and the extract of its fæces appeared to be non-toxic.

that, in the case of guinea-pigs, feeding with bacteria which do not damage adult animals also produces no infection in the newly-born. Casein, white of egg, and hæmolytic serum did not appear in most cases to traverse the intestinal wall in newly-born guinea-pigs unchanged; and the same was true of diphtheria and tetanus toxine. Uffenheimer is, however, careful not to generalize from results obtained from only one species of animals, or to apply them to the human subject. He is even disposed to admit that the passage of protective substances from the intestine into the blood may take place during the first few days of life in infants. Salge's (106) experiments, which negatived the absorption of diphtheria toxine given by the mouth, and those of Hamburger and Speck (106A), disproving the passage of albumin into the blood, and, further, the results of Schütz and von Zaremba, quoted above, all point in the same direction. So that a series of important experimental results are arrayed against Behring's idea of immunizing newly-born animals against tuberculosis via the intestine.

III.—ABSORPTION.

A.—PROTEIN.

The question whether protein bodies which the infant takes in the milk are completely absorbed, or are in part undigested and excreted with the fæces, has been long considered an important one; especially as—since Liebig's researches many years ago—protein alone has been deemed capable of repairing the wear and tear of the vital processes, the nitrogen-free bodies being merely regarded as fuel. Accordingly, the value of protein must be especially high for a growing organism. When, later, the significance of fat and carbohydrate in metabolism was brought into greater prominence, the question of the absorption of nitrogen still remained of great interest. Experiments were easily made for determining the nitrogenous balance-sheet. The amount of nitrogen absorbed was held to be an indicator of the functional activity of the intestine, and it was supposed that pathological conditions in infants would be explained by variations in absorption.

Before an adequate technique for conducting metabolism experiments had been elaborated, attempts were made to determine the nitrogen content of the dried fæces, and its variation under varied diets and under pathological conditions. The first to institute a complete and systematic investigation was Tschernoff (107). He found in breast-fed children 5·2 per cent. nitrogen in the dried fæces; in those from the artificially fed, 6·0 per cent. The nitrogen content in the stools was diminished in diarrhœa, owing to the increased excretion of fat which took place at the same time. Lange (108) found in fourteen children with normal stools 2·78 per cent. nitrogen, and in the stools of dyspeptics, 1·98 per cent. nitrogen; but in another case which Lange investigated in conjunction with Berend the nitrogen content of the fæces, in spite of the presence of diarrhœa, appeared to be 7 per cent.

This method of examining the fæces only gives no data for estimating the amount of absorption. Especially is it inadequate to support the view, so energetically maintained by Biedert, that the casein of cow's milk is difficult to digest.

In one sense the question of the digestibility of milk protein can only be answered by the quantitative estimation of the total intake and output. But since a method has recently been elaborated which allows of the urine and fæces being separated and collected without loss, we will consider first a relatively small number of metabolism experiments, which are, however, sufficient to clear up considerably the question of protein absorption in healthy and sick infants ; more especially the question whether the absorption of protein by sick infants is impaired in such a way that it hinders recovery and restoration, or leads to a condition of hunger in the organism.

With regard to the healthy child, we must refer to the careful, critical review by Czerny and Keller. Here we will only extract a few examples to show that the absorption of protein in healthy children is remarkably good, whether they are fed naturally ar artificially :

Human Milk.

Author.	*Age.*	*Duration of Experiment.*	*Weight.*	*Increase.*	*Nitrogen Content.*		*Percentage Absorbed.*
					Food.	Fæces.	
		Days.	Gm.	Gm.	Gm.	Gm.	
Michel, II. (109)	11 days	3	4,400	+40·0	1·870	0·0903	95·30
Keller, VIII. (110) ..	2 months	5	4,350	+28·0	1·875	0·2441	87·00
Rubner and Heubner (111)	2¼ ,,	9	5,220	+33·0	0·996	0·1740	83·12
Michel and Perret (112) ..	3 ,,	3	4,725	+29·0	1·675	0·1760	89·50

Cow's Milk and Milk-Sugar.

Author.	*Age.*	*Duration of Experiment.*	*Weight.*	*Increase.*	*Nitrogen Content.*		*Percentage Absorbed.*
					Food.	Fæces.	
	Months.	Days.	Gm.	Gm.	Gm.	Gm.	
Keller, XII. (110) ..	2⅔	5	4,900	− 6·0	2·2260	0·1405	93·7
Rubner and Heubner (113)	7½	7	7,570	+21·7	4·3956	0·2810	93·5

The absorption of nitrogen in healthy children varies from 83 to 95 per cent. There is no difference in this respect between natural and artificial feeding. Possibly, indeed, the absorption of protein from cow's milk is better than that from human milk, in spite of its higher nitrogen content. The application of these results to sick children raises a difficulty, inasmuch as metabolic disturbances in infants are of various kinds, and that there is, as yet, a divergence of opinion among

certain authors as to the nature of the disturbances of nutrition. For this reason, the results of competent investigators vary considerably, and are difficult to compare with one another.

There are at present about forty metabolism experiments on children suffering from the most varied disturbances of nutrition, and under manifold experimental conditions (114 to 122).

All these experiments cannot be mentioned here. Only those will be admitted within the range of this discussion which were undertaken with a definite object in view. Five experiments are to hand on the absorption of nitrogen in breast-fed children, the subjects of gastro-intestinal disease [Keller, Freund].

Author.	*Age.*	*Duration of Experiment.*	*Weight.*	*Increase.*	*Nitrogen Content.*		*Percentage Absorbed.*
					Food.	Fæces.	
	Months.	Days.	Gm.	Gm.	Gm.	Gm.	
Keller, V. (110) ..	2¼	5	3,190	−22·0	1·132	0·1707	84·9
,, VI. (110) ..	2½	5	3,300	+28·0	1·600	0·3040	81·0
,, XI. (110) ..	4	5	3,630	+14·0	1·5259	0·4328	71·7
Freund, I. (116) ..	4½	4	4,500	+ 7·5	1·2050	0·1750	85·5
Keller, II. (110) ..	5	5	4,190	+22·0	1·5116	0·2898	80·9

Keller's cases refer to children who were ill when artificially fed, and then were nursed by a wet-nurse; Freund's case was breast-fed throughout. The absorption of nitrogen was, on the whole, good; only in Case XI. of Keller's was the absorption poorer without an explanation being forthcoming from the clinical condition of the child.

Author.	*Age.*	*Duration of Experiment.*	*Food.*	*Weight.*	*Increase.*	*Nitrogen Content.*		*Percentage Absorbed.*
						Food.	Fæces.	
	Months.	Days.		Gm.	Gm.	Gm.	Gm.	
Keller, II. (118)	8	5	One-half cow's milk	4,020	+ 1·0	1·4975	0·0616	95·9
Keller, III.A (119)	9	5	One-third cow's milk	3,960	+48·0	1·2454	0·0846	93·2
Keller, IX. (110)	10	5	Whole milk	4,380	+48·0	4·7754	0·2957	93·7
Rubner and Heubner (113)	3½	4	Diluted cow's milk+ milk-sugar	2,935	− 1·0	2·1080	0·386	82·0
Lange and Berend, II. (114)	6	5	Two-thirds milk+ milk-sugar	6,005	−31·0	4·5721	0·9428	79·4
Keller, III.B (119)	9¼	4	One-third milk+ maltose	3,780	−17·5	0·8960	0·0687	92·3
Freund, III.C (116)	8	5	One-third to one-half milk + gruel	5,236	+17·0	3·1210	0·1520	95·1
Keller, I. (120)	8	6	Malted meal	5,370	−40·0	2·3443	0·5172	81·6

The metabolism experiments with artificial feeding mainly relate to chronically sick children who, though free from acute disturbance at the time of the experiment, were recognised as out of health owing to failure to put on weight, or more or less obvious symptoms of atrophy.

In most cases the nitrogen absorption was good in spite of the disturbance of nutrition; in some it was better than in healthy breast-fed children.

Nevertheless, the absorption of nitrogen is not equally good in all cases. The figures, as shown in the following table, indicate deficient absorption of nitrogen.

Author.	*Age.*	*Duration of Experiment.*	*Food.*	*Weight.*	*Increase.*	*Nitrogen Content.*		*Percentage Absorbed.*
						Food.	Fæces.	
	Months.	Days.		Gm.	Gm.	Gm.	Gm.	
Bendix (115) ..	4	5	One-half milk+ milk-sugar	3,830	—	3·424	0·9600	72·0
Lange and Berend, III. (114)	6	3	Two-thirds milk+ milk-sugar	4,770	−23	3·8491	1·4733	61·9
Baginsky, I. (121)	?	4	Milk+ gruel	?	−25	1·4760	0·7830	47·3
Baginsky, II. (121)	?	5	—	—	−32	—	—	63·0
Rubner and Heubner (113)..	3½	3	Only gruel	2,990	−23	1·0210	0·448	56·2
Freund, III. (117)	2	4	Malted gruel	3,220	−40	1·7800	0·816	54·2

The results shown in this table require some explanation.

The cases of Bendix, Lange, and Berend and Freund had all during the period of the experiment more or less diarrhœa, and it is not remarkable that, owing to the increased peristalsis, absorption went on less satisfactorily. The cases of Baginsky, as also one reported by Poppi (122), in which 18·27 to 43·81 per cent. of the nitrogen in the food was lost in the fæces, may be explained on the grounds that they were not reported with sufficient care.[1] The diminished nitrogen absorption in the experiments of Rubner and Heubner are explained by the fact that the child under observation had no milk, but only cereals, the absorption of which is, without doubt, less complete than that of milk. And since the child took this in relatively small amounts, it must have lost weight very rapidly owing to the small intake of nitrogen.

We have mentioned above that diarrhœa exerts an unfavourable influence on nitrogen absorption. Thus we see nearly always a raised nitrogen excretion in the stools of children suffering from frequent diarrhœa. How far this is due, however, to quickened peristalsis, and how far to increased manufacture and outpouring of the nitrogenous intestinal secretion, we are unable to decide.

[1] Heubner (123), moreover, briefly alludes to two cases of marasmus in which in three daily estimations 43·7 and 54·4 per cent. nitrogen was lost in the evacuations.

The absorption of nitrogen is decreased by the presence of carbohydrates as well as by diarrhœa. At any rate, in nearly all cases in which carbohydrates (milk-sugar, maltose, saccharose, cereals) were added to the milk the nitrogen lost in the fæces was increased. The cause of the bad influence of carbohydrates on absorption of nitrogen, which was first insisted on by Keller, Heubner, and Bendix, though denied by Moro and Schlossmann (7) without experimental proof, lies in the increased peristalsis due to fermentation products, the increased intestinal secretion, and the less complete breaking down of the cereal nitrogen.

Fat also appears to influence nitrogen absorption unfavourably. Although there are at present no reliable experiments available, yet it is probable, from some urinary researches which will be mentioned later, that increased quantities of fat diminish the nitrogen absorption ; hence the proportion of nitrogen in the urine sinks under the influence of increased fat intake [Czerny and Keller, Steinitz].

To briefly recapitulate the conclusions to which the foregoing statistics on the nitrogen absorption in sick children lead, it appears that nutritional disturbances interfere with it but slightly or not at all. On an exclusive milk diet, and to a certain extent also when carbohydrates are added, absorption may be quite good, provided a sufficient amount of nitrogen is converted into the intermediate metabolic products. In diarrhœa it sometimes falls considerably, but always remains high enough for a sufficiency of nitrogen to reach the circulation.

It cannot be denied that disturbances in nitrogen absorption occur in children who are seriously ill. It appears especially that the intestine of marasmic children under certain conditions loses much of its power of absorption [Baginsky, Poppi, Heubner] ; but, generally speaking, there is good absorption from the intestine in marasmus [Bendix, Freund]. Still, it is certainly not possible to regard disturbances of the absorptive power of the intestine as the primary cause of chronic nutritional diseases and marasmus, as does Baginsky. Marasmus can occur even with the best absorptive powers, and, on the other hand, we often see recovery and repair take place in marasmics whose absorptive power is below the average—as, for example, when malted foods are used.

B.—FAT.

The amount of fat in a normal infant's stool is apparently very variable. According to most authors [Weyscheider, Biedert, Uffelmann, Kramstyk, Tschernoff, and others], it amounts to from 9 to 35 per cent. of the dry substance. Shaw and Gilday (210) find that 4 per cent. in nurslings, and 5 per cent. in bottle-fed infants, of the fat ingested appears in the fæces. The fatty compounds appear as fatty acids chiefly, but neutral fat and soaps are also present ; the soaps are increased in artificially-fed children, and in infants with diarrhœa, and after a low fat intake. In the cases first described by Demme (124)—and called by Biedert (125) fat diarrhœa —the amount of fat in the stools reached 67 per cent. (exclusive of fatty acids combined as soaps). In these cases, which occurred both in breast

and bottle-fed children, the stools were greyish and soapy in appearance, and a large proportion of fat droplets could be easily seen under the microscope. How far, however, there was a disturbance of fat absorption —that is, how much of the fat given as food was excreted in the fæces— is not yet determined.

Although normally the amount of fat in the stools—which Keller (110) has shown from the stools of fasting children to be nearly all derived from food—is quite considerable, yet the absorption seems remarkably good. It amounts to from 90 to 98 per cent. of the fat given as food (126).

Our knowledge of fat absorption in marasmics and children with gastro-intestinal disease is much less complete. Here we have only the following figures :

	Fat Absorbed per Cent.
Bendix (115)	59·09
Lange and Berend, I. (114)	75·2
Lange and Berend, II. (114)	86·5
Rubner and Heubner (*a*) (113)	84·46
Rubner and Heubner (*b*) (113)	56·9

We must note that the figures of Berend and Lange, and Rubner and Heubner, for the absorption of fat are too high, because only the fat in the fæces was estimated, and not the soaps. This little table shows, then, that in children suffering from gastro-intestinal disease there is a disturbance of fat absorption, which is of all the more importance for the pathology of metabolism in infants in that it eventually interferes with the assimilation of nitrogen. The latter consequence, as we have seen, is of a secondary character, and is never so great that the organism suffers from the want of nitrogenous material. We find, even when the nitrogen absorption is relatively very incomplete, that some is retained. Thus disturbances of fat digestion, as we shall see in dealing with the absorption of alkalis, are primarily hurtful to the organism, owing to the circumstance that the fat exercises an influence on the excretion of mineral matter, and especially on the evacuation of fixed alkalis by the intestine.

C.—CARBOHYDRATES.

In the normal stools of healthy infants sugar is either absent, or only present in very small amount [Wegscheider, Uffelmann, Blauberg]. It must not, however, be concluded from this fact that sugar is completely or almost completely absorbed. According to our present knowledge a certain, by no means negligible, amount is decomposed by the fermenting agencies in the intestine, and escapes absorption. The products of its decomposition serve to maintain the acid reaction of the intestinal contents, which, for their part, secure a normal bacterial growth and normal peristalsis of the intestine. We do not yet know how far milk-sugar, the only carbohydrate present in the natural diet of infants, is absorbed, and our knowledge is still slighter regarding the absorption of

other kinds of sugar, or of cereal foods (especially) which have to be converted into sugar before absorption.

The first experiments undertaken to ascertain the fate of carbohydrates in the intestine originated with Heubner and Carstens (127, 128). Starting from the clinical observation that a temporary diet of gruel is accompanied by remarkably good effects in infants with gastro-intestinal disorders, the two authors endeavoured to determine how much of the cereal diet was absorbed. As they assumed that all the carbohydrate given which could not be recovered from the fæces was absorbed, they concluded that even in extremely ill or moribund infants the percentage of absorption was from 90 to 100. This astonishing result was criticised by Biedert (71), and in particular by Schlossmann (14), who by test-tube experiments was able to show that starch solutions were broken down by fæcal particles, and by pure cultures of *B. coli* and *B. lactis aerogenes*, so that it was incorrect to conclude that all starch not recoverable from the intestine was absorbed. Heubner (129), however, criticised Schlossmann's results, on the ground that he had created experimental conditions which did not exist in the actual contents of the intestine, and that the part played by the intestinal bacteria in decomposing the ingesta was but slight. It must, however, be allowed that the influence of the fermentative bacteria, which Heubner and Carstens did not take into account, ought certainly not to be overlooked, as the following investigations by Hedenius (61) show. Hedenius also turned his attention to the fate of cereal foods in the gastro-intestinal canal of sick infants. He fed these infants with milk mixed with wheat flour, oaten gruel, a decoction of biscuit, and also with Keller's malt extract, and measured the amount of carbohydrate ingested, the amount in the stools, and their acidity. He found that when simple gruels were used, less carbohydrate was always found in the stools than with complicated mixtures (malt extract and biscuit), and that in the former case the acidity of the fæces was also less. Hedenius never found more than 8 per cent. of the ingested carbohydrate in any case, and it was only the slightly variable acidity of the fæces which indicated a variation in the carbohydrate absorption.

In concluding the discussion of the absorption of sugar in the infant's intestine, we will briefly consider the form in which it enters the circulation. We know that a ferment is secreted in the wall of the intestine which changes milk-sugar before its absorption into dextrose and galactose—namely, lactase. This ferment was detected by Pautz and Vogel (129A) and by Orban (130) in the intestines of new-born infants, and the latter also found it in the fæces of healthy infants. Orban observed the disappearance of lactase in children with severe gastro-intestinal disorders. We know from numerous observations [*e.g.*, F. Voit (130A)] that when milk-sugar passes directly into the circulation it may be completely recovered in the urine; it would be reasonable to suppose that when, owing to the want of lactose-splitting ferment, milk-sugar was absorbed unchanged, a lactosuria would be set up. This view has received support from an observation made by Grosz (131), who, though never able to detect milk-sugar in the urine of healthy infants, found it in the urine of

those suffering from gastro-intestinal complaints, in which probably there was an absence of lactase in the intestine. But the matter is not really so simple. Langstein and Steinitz (131A), who repeated Orban and Grosz's experiments, found lactase in the stools of infants even when sugar was being excreted in the urine. Moreover, this sugar was shown by the fermentation test, the mucinic acid test and the phenylhydrazin test to be not in all cases lactose, but sometimes galactose. To explain the lactosuria when lactase was present in the intestine, Langstein and Steinitz suppose that in children with gastro-intestinal disease some disproportion exists between the action of the lactase, which is always present in the intestine, and the amount of lactose awaiting absorption; or that some milk-sugar, through functional or anatomical lesion of the wall of the gut, passes through before it is completely broken up, and is excreted in the urine as an intermediate metabolic product. But in very severe cases galactose, a product of the decomposition of milk-sugar, is also excreted in the urine, which appears, according to the researches of Hofmeister (131B) and Luzzatto (131C), to be especially difficult to oxidize.

D.—MINERAL MATTER.

Investigations as to the absorption of mineral matter have not the same importance for metabolism as those on the combustible foods. The reason is that the intestine is not only the place of absorption for a certain portion of the mineral substances, such as lime, magnesia, and partly, too, of the alkalis, but also the place of their excretion; so that analysis of the fæces gives no information as to whether the salts present arise directly from the food, or have already taken part in the metabolism of the body. We need not, therefore, quote the few existing experiments on the metabolism of mineral matter in healthy [Michel, Michel and Perret, Rubner and Heubner, Blauberg] and in sick children [Rubner and Heubner]; nor need we avail ourselves of the elaborate, but somewhat barren, investigations of Blauberg (121, 133) on the absorption of certain constituents of ash, seeing that no conclusions—as Blauberg himself admits—can be drawn therefrom. Here, then, we shall record certain researches only on the absorption of mineral matter, which were instituted, not on specially selected children, but in order to elucidate particular questions under various experimental conditions. These are nearly all connected with children suffering from gastro-intestinal diseases.

1. Calcium.

The question of the absorption of lime in the infant's intestine is interesting owing to its relation with the etiology of rickets. Ever since Söldner (134) showed that cooking milk converts the soluble into insoluble lime salts, and that these latter are not only useless for rennet coagulation, but also not suitable for absorption, sterilization of milk has been suspected of favouring decreased lime absorption and a conse-

quent occurrence of rickets. Without discussing the correctness of these views, we will merely quote certain observations concerning the difference in absorption in fresh and uncooked milk. According to Fritz Voit's (135) experiments, which have been frequently confirmed, lime is not only absorbed, but also excreted in the intestine; it is, therefore, hardly possible to calculate the amount of lime absorbed into the circulation. We shall quote here the figures derived from the percentage of lime in the urine, the variations in which either exactly, or almost exactly, correspond to the varying amounts absorbed.

Arndt (136), and Cronheim and Müller (137), have investigated the metabolism of lime on a diet of fresh and boiled milk. Only one experiment can be quoted from the former, as in this one alone were the experimental conditions exactly similar in both series.

Author.	*Age.*	*Duration of Experiment.*	*Food.*	*CaO.*			
				Food.	Fæces.	Absorption per Cent.	Assimilation per Cent.
	Months.	Days.		Gm.	Gm.		
Arndt (*a*)	5½	4	Malted food (boiled goat's milk)	0·6115	0·1852	69·7	66·73
Arndt (*b*)	5½	4	Malted food (raw goat's milk)	0·7460	0·3681	50·7	48·15
Cronheim and Müller (*a*)	6	4	Three-quarters milk + milk-sugar (boiled)	1·2750	1·1910	6·59	5·75
Cronheim and Müller (*b*)	6	4	Same raw	1·2730	1·094	14·12	13·33
Cronheim and Müller (*a*)	4	4	Same cooked	1·3520	0·918	32·12	30·87
Cronheim and Müller (*b*)	4	4	Same raw	1·3510	0·923	31·65	30·45

The table indicates that there is no appreciable difference between the absorption and retention of lime (or of magnesia) on a diet of fresh or sterilized milk. Cronheim and Müller, as a result of these researches, are against the use of sterilized milk, because the boiling has an unfavourable influence on the breaking down of lime; but this is not to the point. From these figures an exactly opposite conclusion might equally well be drawn.

2. Alkalis.

On the absorption of alkalis in healthy children, naturally and artificially fed, Blauberg's (132, 133) researches are pre-eminent; but our knowledge of the part played by alkalis in the intestine of children with gastro-intestinal affections is based on a single series of experiments by Steinitz (138). This is concerned with the influence excreted by the fat in milk on the amount of alkalis excreted by the intestine.

Keller (139) has established an increased excretion of NH_3 in the urine in infants with gastro-intestinal diseases so completely dependent

upon alimentary conditions that it always accompanies an increase of fat in the diet. He has also shown (53) that any deficient conversion of ammonium salts and other nitrogenous products of protein digestion into urea could be excluded. We are, therefore, compelled to regard increased ammonia excretion by the kidneys as the expression of an acidosis, and to take the ammonia as an index of the acidity. We shall deal with this condition of acidosis later. Here we are concerned solely with the discussion of the intestinal processes which co-operate in its production. The amount of NH_3 excretion, which is the index of acidosis, depends to a certain extent on the alkalinity of the tissues as a whole; that is to say, in so far as, under conditions of diminished supply, every factor which withdraws alkalis from the general circulation in any form produces an increased NH_3 excretion. Now, in milk diet there is a very small supply of alkali; we see, therefore, that an increased alkali excretion by the intestine, howsoever produced, occasions a decrease in the alkalinity of the body and an increase in the NH_3 in the urine.

Steinitz was able to show that the increased NH_3 excretion on a milk diet rich in fat was a consequence of the removal of alkali via the intestine. The following figures are taken from his experiments:

	Duration of Experiment.	*Food.*	*Fat Content in Food.*	*Alkalinity.*			*Lime in Fæces.*	*N : (NH_3) in Urine per Cent.*
				Food.	Fæces.	Absorption per Cent.		
	Days.		Gm.	Gm.	Gm.		Gm.	
Experiment I. (*a*) ..	3	Two-thirds	1·0	1·359	0·337	75·2	0·466	3·8
(*b*) ..	3	milk	4·8	1·293	0·707	42·5	0·413	7·7
Experiment II. (*a*)	4	One-half	1·45	1·133	0·2655	76·6	0·355	4·9
(*b*)	3	milk	5·28	1·008	0·8013	20·5	0·412	14·5
Experiment III. (*a*)	3	One-half	1·2	1·107	0·582	47·5	0·387	8·2
(*b*)	2½	milk	5·1	0·916	1·62	—	0·216	14·3

Raising the supply of fat increased the excretion of fixed alkali by the intestine (the increased excretion mainly concerned the sodium). It is not yet known in what manner the fat causes a loss of alkali through the bowel in infants. It is possible that the alkali is excreted as a potash or sodium soap. Keller (140), who investigated the influence of fat on the separation of soaps in the stools of infants suffering from gastro-intestinal disease, could not answer this question, owing to the way he arranged his experiments. On the other hand, Freund's (140A) observations make it probable that, under the influence of fat, there is an increase in the soaps—or, at any rate, in the calcium soaps—in the stools. The total excretion of lime was not increased by the ingestion of fat, either in Freund's or in Steinitz's experiments; but the circumstances were altered so that a part of the lime, instead of being excreted as calcium phosphate, which occurs when the diet is poor in fat, was used up for the formation of soap, and the insoluble soap in the stools was increased.

3. Chlorides.

Our knowledge of the absorption of chlorides in the infant's intestine is limited to Freund's (116) experiments. He found that the more watery the stools, the less chloride was absorbed. His explanation of this fact was that in diarrhœa a salt solution rich in sodium, and not mere water, is poured out into the bowel. According to this author, a diet of fat-rich milk increases the amount of chlorides in the fæces.

4. Phosphorus.

The question of phosphorus absorption may be considered in connection with the absorption of inorganic materials, although a considerable part of the phosphorus exists in food in organic form, and is excreted as such in the fæces. This portion of the phosphorus excreted in the stools has been invested with special importance by Knöpfelmacher (141). This author started with the idea of estimating the amount of residue left by the digestion of casein by the amount of organic phosphorus in the fæces. As he found the ratio N : organic P in stools from mother's milk and in meconium much greater than in stools from cow's milk, he thought he had shown that the casein of human milk was completely digested, whereas the casein of cow's milk left behind a residue rich in phosphorus. More recent researches by Müller (142) and Knöpfelmacher (143) himself showed that this conclusion, which was based on faulty experimental technique, was erroneous. It appears that the ratio of N : organic P is exactly the same in natural and artificially fed children—at any rate, during health. As to sick children, there is no experimental evidence.

The total absorption of phosphorus varies within wide limits both in healthy [Michel, Michel and Perret, Keller, Blauberg, Schlossmann (143A)] and in sick children [Keller, Freund, Blauberg, Schlossmann]. In general, it is better in healthy than in sick children, in whom it is occasionally extraordinarily low [Blauberg]. Whether in these cases there is really a poor absorption of the organic phosphorus in the food, or an increased excretion of phosphates into the intestine, or a decreased absorption of inorganic phosphorus, is unknown, as also are the conditions on which phosphorus depends for its absorption. The amount of phosphorus furnished by the intestinal secretions plays an important part, and no doubt, under pathological conditions, can cause a not inconsiderable increase.

Author.	*Food.*	$N : P_2O_5$.	
		Food.	Fæces.
Michel, I.	Woman's milk	5·10 : 1	3·80 : 1
Keller, IV...	,, ,,	5·90 : 1	4·20 : 1
Michel and Perret	,, ,,	6·30 : 1	2·40 : 1
Keller, IX.	Cow's milk	2·40 : 1	0·33 : 1
Blauberg	Diluted cow's milk+ milk-sugar	2·90 : 1	1·00 : 1
Freund, III.	Malted food	2·75 : 1	1·60 : 1

In all cases the residue of phosphorus in the fæces is greater than the nitrogen ; it follows that the ratio of nitrogen to phosphorus is always smaller than in the food, both in naturally and artificially fed children, and in conditions of both sickness and health. According to Knöpfelmacher and Müller's experiments, we may assume that this surplus of phosphorus in the fæces originates in inorganic, and not in organic, compounds of phosphorus.

Tunnicliffe, in a recent review on the subject, comes to the following conclusions, as the result of careful metabolism experiments on two healthy children, aged two years and two years and ten months. In a healthy child, the inorganic phosphates (calcium phosphate) are not retained, and do not influence nitrogenous metabolism when added to food, whereas organic phosphorus (sodium glycero-phosphate of casein) is practically entirely assimilated, and also increases the amount of nitrogen retained in the body. Clerc and Cook have shown that the addition of inorganic phosphorus to a diet poor in that element results in a negative phosphorus and nitrogen balance. Organic phosphorus causes increased nitrogen metabolism, and raises the phosphorus and nitrogen retention. When the diet contains the normal amount of phosphorus, no increased nitrogen retention follows the administration of organic or inorganic forms, but addition of large amounts of the former is not followed by its increase in the urine.

IV.—FATE OF THE FOOD-STUFFS OUTSIDE THE INTESTINAL TRACT.

The fate of the food-stuffs which have been absorbed into the general circulation reveals one of the principal differences between the healthy adult and the child. Whereas the former, in a condition of metabolic equilibrium, only uses the ingested food-stuffs to replace used-up and dead cells, to furnish secretions and to produce heat, the young organism is always producing new cells and growing. And it is not only the healthy child in normal surroundings that has the power of assimilating the materials it ingests, and of using them for the building up of the tissues : children suffering from gastro-intestinal diseases, and even marasmics, manage to grow to a limited extent, even when the weight remains for a time the same, or actually decreases.

A discussion, therefore, of the intermediate metabolic processes in children must be divided into two sections, one being devoted to the increase in size and growth, and the other concerned with the destructive or retrogressive changes in the food-stuffs.

A.—ASSIMILATION.

1. Protein.

Our knowledge of the assimilation of protein in healthy infants is obtained from the collective data of Czerny and Keller.[1] In all their cases there was a considerable assimilation of nitrogen. This, in the case of the young breast-fed child, amounted to more than 75 per cent. of the ingested nitrogen, and in one case (Michel, II.) reached almost 90 per cent. In artificially fed children the assimilation, expressed in percentage of the ingested nitrogen, is not so high—partly, at any rate, due to the fact that the proportion of nitrogen in the food is much greater. In absolute figures the assimilation in children fed with cow's milk is equal to that found in breast-fed infants.

We must note here that the figures for the nitrogen balance obtained by most authors make no approach to absolute accuracy. For, with the exception of Rubner and Heubner (111, 113), who estimated in their experiments the nitrogen lost by the sweat, no authors have taken into consideration the excretion of nitrogen by the sweat, hair, epidermis, and saliva; and this is also true for the investigations with sick children to be discussed later.

If we turn to the results obtained from investigations of the metabolism of sick children, it appears that in most of these assimilation of nitrogen goes on. We know of but few experiments in which the nitrogenous equilibrium is negative.

Author.	*Age.*	*Duration of Experiment.*	*Food.*	*Body-weight.*	*Daily Increase.*	*Nitrogen Content—*			*Nitrogen Balance.*
						Food.	Urine.	Fæces.	
	Months.	Days.		Gm.	Gm.	Gm.	Gm.	Gm.	Gm.
Keller, IIIA. (119)	9	5	One-half milk	3,960	−48	1·2454	1·7008	0·0846	−0·540
Rubner and Heubner (113)	3½	3	Malted meal	2,990	−23	1·0210	0·882	0·448	−0·309
Baginsky, II. (121)	—	5	Milk+ gruel	—	−32	—	—	—	−1·540
Freund (117)	2½	5	One-half milk	3,380	−32	1·1400	1·026	0·248	−0·134

These figures require no further commentary, as it is easily understood, *a priori*, that with loss of body-weight must go a disappearance of protein and an increased excretion of nitrogen. But in these investigations even the circumstances are not so simple that we can say that the decrease of body-weight can be estimated from the loss of nitrogen. Thus, in Baginsky's case, we have just the same changes in weight as in Freund's, but the loss of nitrogen is twelve times greater. The assimilation of

[1] Czerny and Keller (2).

nitrogen in healthy children is generally proportionate to the body-weight; in pathological cases, however, as we shall see when discussing the assimilation of water, it is absolutely no index of normal growth.

A negative balance we only find in the most exceptional cases; in nearly all the cases recorded hitherto assimilation of nitrogen can be shown whether the body-weight is rising or falling.

The first alternative we need not stop to discuss. It is clear that sick children, and more especially those with chronic illnesses, may put on protein, together with all other materials essential to growth, if they become convalescent during the period under observation, of which condition a rise in weight is a specially unmistakable indication. Here belong a series of experiments by Keller and by Freund, and also one observation by Bendix, and one by Lange and Berend.

In some of these experiments there is no want of correspondence between the increase in body-weight as actually observed and that calculated from the amount of nitrogen assimilated.

But the explanation of the second alternative, of which we have a whole series of examples, is more complicated; in these we have no inconsiderable assimilation of nitrogen, though the weight remains stationary or falls.

To quote some examples:

As the following table shows, in a series of experiments the weight remained constant, or there was considerable fall, though nitrogen was being assimilated. How can this want of correspondence between assimilation and body-weight be explained? In the present position of our knowledge we rightly refer the assimilation of nitrogen in a growing organism to growth and the building up of new cells. It appears, therefore, that all these children are actually putting on protein—a fact which is supported by Camerer's observation that children, in spite of wasting and atrophy, nevertheless grow noticeably in height.

Author.	*Age.*	*Duration of Experiment.*	*Food.*	*Body-weight.*	*Daily Increase.*	*Nitrogen Content—*			*Nitrogen Balance.*
						Food.	Urine.	Fæces.	
	Months.	Days.		Gm.	Gm.	Gm.	Gm.	Gm.	Gm.
Keller, V. (110)	2¼	5	Mother's milk	3,190	−22·0	1·132	0·6937	0·1707	+0·2676
Keller, III. (110)	5½	5	One-half cow's milk	3,960	−12·5	2·0500	1·6056	0·2752	+0·1692
Rubner and Heubner (113)	3½	4	Diluted milk+ milk-sugar	2,935	−1·0	2·1080	0·7560	0·3860	+0·9660
Bendix (115)	4	5	Two-thirds milk+ milk-sugar	3,830	—	3·4240	1·7140	0·9600	+0·7500
Lange and Berend, II. (114)	6	5	Ditto	6,005	−31·0	4·5720	2·8452	0·9428	+0·8840
Freund, III. (117)	2	4	Malted food	3,220	−40·0	1·7800	0·4870	0·8160	+0·4770
Keller (120)	8	6	Ditto	5,370	−40·0	2·3443	1·4963	0·4310	+0·4170

In this case, however, the loss of body-weight may be merely due to simultaneous loss of fat or water. We must, indeed, assume that in a large number of cases a child suffering from gastro-intestinal diseases, when assimilating protein and building up cells, in spite of a stationary or falling body-weight and a failure to thrive, must be losing other material, and especially fat. In this manner the child becomes poor in fat, but otherwise maintains his percentage composition, so that we can understand why the chemical analysis of the body after death shows the same ratio between nitrogenous material and the content in water and ash. We must, of course, not conclude that in sick children an increase in nitrogen may take place which would change the composition of the organism. Variations in the amount of water in children with gastro-intestinal diseases have been definitely established by Freund's (117) experiments.

The question of the influence of carbohydrates on the assimilation of protein demands special attention. It is *a priori* to be expected that the influence would be the same as in adults and animals, but in view of the important part which carbohydrates play in the nutrition of children suffering from gastro-intestinal disease, in that they enable fat and protein to be retained to a much greater extent, we must consider this point in further detail.

Exact metabolism experiments on this point in children with chronic gastro-intestinal disease have only been made by Keller (119). We will quote the result of one of his four series of experiments, which all agreed in showing that the influence of maltose on nitrogen metabolism was to increase the assimilation of that element.

	Age.	*Duration of Experiment.*	*Food.*	*Body-weight.*	*Daily Increase.*	*Nitrogen Content—*			*Nitrogen Retention.*	
						Food.	Urine.	Fæces.	Gramme.	Per Cent.
	Months.	Days.		Gm.	Gm.	Gm.	Gm.	Gm.		
IV. (*a*)	2½	6	One-third milk	3,540	−20	1·2782	1·0717	0·1980	0·0085	0·7
IV. (*b*)	2¾	7	One-third milk + 40 grammes maltose	3,500	+0	0·8707	0·6290	0·1305	0·1108	12·7

The child in this experiment during the time that it was taking malt put on 12·7 per cent. of the ingested nitrogen, in spite of the fact that the amount of nitrogen in the diet was only two-thirds of that in the first period; when on milk alone, it merely remained in nitrogenous equilibrium.

Of the action of other carbohydrates on nitrogenous metabolism we have no experimental evidence, but we know from clinical experience that maltose occupies a special position for infants; and we may therefore, perhaps, conclude that cereals and other forms of sugar do not exercise the same protein-saving action as does this one.

2. Mineral Matter.

On the assimilation of mineral matter in the infant our remarks will be brief, as our knowledge of both its physiological and pathological significance is equally incomplete.

In healthy children, the assimilation of mineral matter in general is good [Michel, Michel and Perret, Rubner and Heubner], and it is also well retained by those suffering from gastro-intestinal diseases. In the few experiments dealing with this matter, which show both the nitrogenous and the mineral equilibrium, we see that both vary concomitantly.

If these results are confirmed by further researches, it will form an additional indication of the fact that assimilation really means the building up of new cells, since it takes place in those proportions, both of nitrogen and mineral matter, which we have learnt from analysis obtain in the bodies of new-born children and those with gastro-intestinal diseases.

Author.	*Case.*	*Food.*	*Nitrogen Balance.*	*Mineral Matter Balance.*
			Gm.	Gm.
Heubner and Rubner Blauberg	Atrophic child	Diluted milk+ milk-sugar and malted meal	+0·928 −0·347	+0·634 −0·399

With regard to the retention of the various mineral substances, as yet too little is known to make any conclusions permissible. On the assimilation of phosphorus, there are only Killer's (110) experiments, in which it is shown that even children with gastro-intestinal disease assimilate phosphorus. Sick children assimilate phosphorus better when fed on the breast. The assimilation of lime is dealt with in the section on absorption.

We shall deal with assimilation of chlorides in connection with that of water.

The assimilation of alkali has hitherto only been investigated by Steinitz (138). He found that, under the influence of a diet rich in fat, not only was the evacuation of alkali by the intestine increased, but in all three experiments on this point the total balance-sheet for alkali showed a loss when cream was given in the diet. He concluded that a diet of milk rich in fat, among other things, exercised a deleterious influence on the metabolism of infants suffering from gastro-intestinal diseases, so that a loss of alkali was set up, and that this prevented the normal growth of the organism, as, according to Steinitz, an increase in body-substance is impossible without a simultaneous increase of all substances appertaining thereto, including, of course, the alkalis.

Stöltzner's cases led him to consider that tetany was associated with a calcium-poisoning. He found a " stasis " in the calcium circulation, and viewed the good results following phosphorus therapy in rachitic

children as due to the favourable influence on the rickety process, and the improvement in the calcium circulation. Cybulski observed a low retention of calcium in the eclamptic stage, and a gradually increased retention in the convalescent period. He therefore attributes the tetany to the poverty of calcium in the central nervous system (216).

Würtz states that iron preparations are necessary when mixed food is given, and that bioferrin exerts good influence on the appetite, Hb, and general condition in the " alimentary anæmia " of children (217).

The iron of human milk is absorbed much better than that of goat's milk. The iron in boiled milk is absorbed better than that of raw milk. The high percentage absorption of the iron in human milk compensates for the slight amount of iron present in ordinary foods. The natural combinations of iron which occur in yolk of egg, spinach, etc., are much better absorbed by children than are the artificial iron preparations (ferratin, etc.) (218).

3. Water.

Full estimations of the equilibrium for water in infants have not yet been made. Rubner and Heubner (111, 113) estimated as exactly as possible the loss of water through the lungs and skin of two healthy infants and one marasmic. Their figures, however, are not sufficient to construct a balance-sheet for water. Camerer (144) reports some valuable and accurate figures on water assimilation, by which it appears that almost 60 per cent. of the daily increase in size consists of water. The ratio, moreover, between the nitrogen, mineral matter, and water put on must be constant.

Our knowledge of the assimilation of water in children suffering from gastro-intestinal diseases is also small. Freund's (117) investigations have yielded the most important results. They consist of clinical observations and experimental researches upon the salt metabolism of infants with gastro-intestinal diseases. Freund thought it possible to calculate from this the water metabolism, because variations in the proportion of water could only occur correspondingly with variations in the proportion of salts. It is the isotonic tissue fluids, however, which are concerned with the gain and loss of body-weight. Salt metabolism, in a certain limited sense, may be taken as an index of water metabolism. The salts in question are the chlorides and probably the alkalis.

Freund observed that when good nitrogenous assimilation was unaccompanied by an increase in body-weight, there was a retention of chlorides. In the same way, there was considerable assimilation of chlorides when, with an unusually large increase in weight, only a slight assimilation of nitrogen could be shown. Here a similar want of correspondence existed between the increase in body-weight and the protein consumption, the former being in excess of the latter.

Both these processes, which are illustrated in the following table, can only be explained by water assimilation. In the first cases (with comparatively excessive nitrogen assimilation) water only slightly replaces the lost fat, for the ratio of the assimilated chlorine to nitrogen is greater

than in breast-fed children, but still relatively small. In the other cases (with comparatively small nitrogen assimilation) water replaces the fat, for the ratio of chlorine to nitrogen is large, even exceeding unity.

Author.	*Daily Increase in Weight.*	*Calculated Protein Increase.*	*Ratio between the Two.*	*Daily Nitrogen Retention.*	*Daily NaCl. Retention.*	*Ratio between the Two (N=1).*
	Gm.	Gm.		Gm.	Gm.	
Michel (109), IV.	+29·00	+32·50	1·1100	+1·084	+0·207	0·190
Freund (116), III. (*c*) ..	+17·00	+31·00	1·8200	+1·032	−0·320	0·224
Freund (116), III. (*a*) ..	+ 8·50	+17·00	2·0000	0·578	+0·217	0·375
Freund and Kreisel (116) (*b*)	+86·70	+19·67	0·2268	+0·659	+0·322	0·489
Freund and Günther (117) (*a*)	+66·25	+14·08	0·2125	0·472	+0·772	1·636

Freund's hypothesis that every abnormal increase in water (that is, one which does not correspond with the estimated protein increase) is accompanied by retention of chlorides points to the chloride metabolism as an indicator for the water exchanges. But the hypothesis is not applicable to all cases—for example, in many of Freund's experiments there was a loss of body-weight which was not accompanied by a corresponding loss of chlorides. The part played by chlorides and also by other salts in metabolism is much too complicated to be explained by this hypothesis in all possible cases.

For the rest, it must be noted that the variations between water and salts in the tissues of children with gastro-intestinal disease are only neglected because in the further process of metabolism they soon tend to approximate to one another. Otherwise it would be impossible to explain the constant ratio of water and salts which is found in the post-mortem estimations of the tissues of children dead from gastro-intestinal diseases.

B.—EXCRETION.

The katabolic products and other excretions of the organism leave the body by various paths. Although the urine and fæces of infants and children have been the object of many investigations, our knowledge of the gaseous excretions of the body—the "insensible perspiration"—is still scanty. We have no essential information concerning this point in healthy infants, let alone those suffering from gastro-intestinal diseases.

The excretion of carbonic acid in newly-born and young children has been investigated by Scherer (145) and others. Scherer found that the gaseous metabolism of respiration was much more active in children than in adults. In proportion to the kilogramme of body-weight, more O_2 was taken up and CO_2 given off in one hour by a child than was the case in a grown man. The respiratory quotient averaged 0·702 in his experiments, as against 0·89 for adults (according to Laves' investigations). One circumstance detracts from the value of these experi-

ments, and that is that they only lasted one hour. This made it difficult to draw, generally, satisfactory conclusions, and the resulting figures could not be considered in relation to diet.

On the other hand, Rubner and Heubner's statistics on the excretion by the lungs and skin are much more exact and valuable. We give a short table of the figures obtained, with the proviso that we can draw no deductions therefrom concerning the differences between sick and healthy children, owing to the small number of experiments available.

Excretion in Twenty-four Hours per Kilogramme Body-weight.	CO_2.	H_2O.
	Gm.	Gm.
Breast-fed child	21·70	36·70
Healthy artificially fed child	25·14	44·39
Marasmic child fed on cow's milk ..	34·21	55·24
The same on malted gruel	29·32	43·20

Excretion per Square Metre per Hour.	CO_2.	H_2O.
	Gm.	Gm.
Breast-fed child	13·5	22·86
Healthy child fed on cow's milk ..	17·3	30·60
Marasmic child fed on cow's milk ..	17·7	23·90
The same on malted gruel	14·7	21·70

Bendix's (115) assumption that in marasmus there is an abnormal increase of gaseous metabolism due to some toxic substance is not borne out by these experiments. This view seems the less permissible, since Poppi (122) concludes from his estimations of the excretion of water in a marasmic child, and the absorption of O_2 and excretion of CO_2 in seven marasmic children, that the excretion of both water and CO_2 was less than under normal conditions. Poppi's subjects of experiment were all in the third (cachectic) stage, while Heubner's were in the second stage. It is impossible to say whether Poppi is right, as, on account of the absence of clinical histories and other important statistical data, the experiments do not permit definite conclusions.

Camerer and others (146 to 149) give tables of the amounts of "insensible perspiration" in children — that is, the CO_2 and H_2O excretion minus the O_2 intake. There are as yet no published experiments upon sick children.

Excretion through the bowel has already been dealt with in the sections on Changes in Food-stuffs in the Gastro-intestinal Canal and Absorption.

Urine.[1]

In a healthy breast-fed child there is a certain normal daily output of urine. Camerer (146) found that for every 100 grammes of nourish-

[1] This section deals only with those constituents of the urine which are definitely characteristic of the processes of Metabolism.

ment ingested, 68 c.c. of urine were excreted, and his results were confirmed by Keller (110). This ratio between food absorbed and the urine excreted varies, especially in sick children. It is obvious that increase in the output of water by the lungs and skin, and especially by the intestine, must exert a great influence on the excretion of urine. Thus in cases of diarrhœa the proportion of water excreted by the kidneys is markedly decreased; and if with severe diarrhœa there is no increase in the intake of water, anuria may supervene. Severe sweating likewise decreases the relative amount of urine. Retention of water in the body also affects the amount of the urine. This factor is of especial influence when for any reason—*e.g.*, when the diet is changed—there is a marked alteration in the water content of the body. Freund (117) has made observations on the metabolism of sick children, arranging his experiments so as to introduce some change in the diet capable of considerably influencing the body-weight. The characteristic examples quoted in the table on p. 870 show that the body-weight rises and falls with the urinary output.

The *amount* of urine passed in twenty-four hours depends, therefore, partly on the amount of food taken, partly on the amount of water excreted by the lungs, skin, and bowels, and partly on the amount of water retained.

The *nitrogen-containing constituents of the urine* have only been the object of investigation in sick children. We have, therefore, no standard below which the amount observed under pathological conditions can be said to fall.

Estimations of the *total nitrogen excretion* have mostly been carried out in connection with the metabolism experiments. The nitrogen excretion is partly dependent on the amount of nitrogen ingested, but also varies with the amount absorbed by the intestine and retained in the organism. In either case the only estimates available are those with respect to the amounts ingested and excreted in the fæces.

Author.	*Food.*	*Body-weight at Beginning of Experiment.*	*Increase.*	*Amount in Urine.*	
				Absolute in c.c.	Percentage of Intake in Food.
		Gm.	Gm.		
Wuttke, I. (3 days) ..	One-third milk+ 1,490 gms. milk-sugar	3,130	−145	1,075	72·1
Wuttke, II. (2 days) ..	1,490 gms. malted soup	2,985	+155	380	25·5
Kreisel, I. (3 days) ..	One-half milk+ 2,910 gms. biscuit	4,880	+260	1,074	36·9
Kreisel, II. (3 days) ..	Three-fifths milk 3,069 gms.	5,140	−160	1,650	53·7

The ratio of urea to the total nitrogen excretion in healthy breast-fed children has been investigated by Camerer (146, 150, 151). Using Hüfner's method, he found 75 to 80 per cent. of the total nitrogen as urea, whereas Camerer junr. (152), in healthy children fed on cow's milk, observed 84 per cent. (Hüfner's method). On the other hand, Pfaundler (153), in a premature, but thriving, breast-fed infant, obtained only 45 per cent. of urea in the total nitrogen (Schöndorff's method).

Urea. — Keller (Mörner-Sjöqvist), Camerer (156) (Hüfner), and Pfaundler (153) (Schöndorff) have estimated the urea excretion in children with gastro-intestinal diseases. One remarkable fact is brought out by all these investigations alike—namely, that in a large series of cases the smaller proportion of the nitrogen leaves the body as urea.

Author.	*Food.*	*Age.*	*Of* 100 *Gms. Nitrogen.*		
			Urea Nitrogen.	NH_3 Nitrogen.	Amido-Acid Nitrogen.
			Gm.	Gm.	Gm.
Keller (53), V... ..	Malt food	4½ months	52·8	21·1	—
Keller (53), VI. ..	,,	6 ,,	60·7	20·2	—
Keller (120) (p. 48) ..	Malted soup	3 ,,	72·4	12·4	—
,, ,, ..	,, ,,	3 ,,	65·6	13·7	—
,, ,, ..	,, ,,	3 ,,	67·4	13·0	—
,, ,, ..	,, ,,	3 ,,	70·0	13·1	—
Pfaundler (153) (Case 8)	One-half cream+ milk	21 days	17·2	30·0	19·1
Pfaundler (153) (Case 27)	Nestlé's food	2½ months	39·4	16·6	24·2
Pfaundler (153) (Case 32)	Two-thirds cream+ milk	3 ,,	57·0	19·6	12·5
Pfaundler (Case 19) ..	,, ,,	1¾ ,,	29·2	17·8	7·4
Camerer (156) (Case A)	—	3 ,,	62·0	15·0	—

Pfaundler's figures are particularly low, Case 8 only showing 17·2 per cent. of urea. As Pfaundler and Camerer themselves admit, these low figures are exceptional, and require more exact confirmation. They were obtained by the Mörner-Sjöqvist method, and this, according to Braunstein (157), gives rather high than low values. The lower figures of Keller may be taken as the most exact at present obtained.

But even if further researches show that the proportion of urea is really smaller, this, as Keller remarks, is not, perhaps, a characteristic in infants dependent on gastro-intestinal disturbances. Keller (154) records estimations of urea in cases of chronic intestinal disease in children fed on diluted cow's milk (also by the Mörner-Sjöqvist method) which gave an average of 80 to 95 per cent.

Diet, doubtless, conditions the particular manner in which the urea is excreted. A diet of malted gruels, perhaps, produces amido-acids, and often nitrogenous substances of similar, but as yet unknown, composition, which would render the lowest figures for urea excretion at any rate comprehensible; but at present Pfaundler's results cannot be completely explained.

The excretion of *uric acid* and the *amido-acids* under physiological and pathological conditions has not yet been investigated. The few

figures which Pfaundler (133) has published on amido-acid excretion are so high (up to 19 per cent. of the total nitrogen excretion) that it appears doubtful if the method employed was reliable.

The excretion of *ammonia* in the urine will be considered later.

Ratio between Chloride and Nitrogen. — This ratio sheds a peculiar light on the distribution of nitrogenous and non-nitrogenous material in the urine. In the experiments of Rubner and Heubner (111, 113), it was shown that the quotient $\frac{C}{N}$ was 1·27 in breast-fed, and only 0·6 in bottle-fed, children (cow's milk). In two cases investigated by Camerer (158), the quotient $\frac{C}{N}$ in breast-fed children was 1·2 and 1·0, and von Oordt (159), as an average of nine experiments, calculates it at 1·127. It appears, therefore, that the quotient $\frac{C}{N}$ in the urine occupies a special position in breast-feeding. Its large size leads us to suppose that in natural feeding substances are excreted in the urine which are either poor in or free from nitrogen, and indicate a peculiar kind of metabolism. But this supposition cannot be maintained. Langstein and Steinitz (202) have shown experimentally that the ratio C : N can only be influenced by diet in so far as the amount of nitrogen in the urine is concerned. It appears that a certain proportion of organic products free from or poor in nitrogen are in every urine dependent on diet. If, then, the diet is rich in nitrogen and the urine contains much urea, the quotient will fall ; if the urine is poor in urea, the ratio C : N will be altered in favour of carbon. The ratios in adults are exactly similar. Here on mixed diet the ratio C : N is 0·72, on vegetable diet and on a diet poor in nitrogen it rapidly rises to 1·01 [Camerer (158)].

To illustrate this point, the following table is appended. It shows that the quotient $\frac{C}{N}$ is roughly inversely proportional to the amount of nitrogen in the urine. On a diet of malted broth the quotient is strikingly high, though the proportion of nitrogen in the urine rises. Here possibly the amido-acids, in which malted broths are especially rich, influence the ratio C : N in favour of the carbon :

Food.	*Nitrogen in* 100 *c.c. Urine.*	*Quotient,* $\frac{C}{N}$.
	Mgm.	
Breast milk	189·3	1·19
One-third milk + milk-sugar	239·3	1·43
Malted broth	281·7	1·36
,, ,, ...	453·1	1·37
One-half milk, one-half gruel + malt	404·0	1·06
Butter-milk	829·8	0·79
,, ...	979·0	0·76
Full milk	1175·0	0·67
,, ...	1292·0	0·68

A portion of the children examined suffered from gastro-intestinal disease, but the pathological condition appeared to have no influence on the quotient $\frac{C}{N}$.

Mineral Substances.—The only substances requiring mention are phosphorus (especially in its relation to nitrogen excretion) and sulphur.

With regard to the *ratio of nitrogen to phosphorus* in the urine of infants, apart from the older and less useful contributions of Zülzer, Lehmus, and Cruse,[1] and the metabolism experiments already quoted with regard to the absorption of phosphorus, the only detailed observations available are those of Keller (160). These show that the ratio N : P in naturally fed children is, on an average, 7 : 1, and in artificially fed children 2 : 1. As the proportion of N : P is 5·5 : 1 for human milk and 2·5 : 1 for cow's milk, it is clear that the proportion of phosphorus assimilated from human milk is greater than that from cow's milk.

Keller also observed that the quotient $\frac{N}{P}$ is smaller on a diet of cream than on a diet of skim milk. The table below contains some of Keller's results.

The quotient $\frac{N}{P}$ in the first period averaged 1·85, and rose in the skim-milk period to 5·66. Freund (161) confirmed this point as to phosphorus excretion, and also added the observation that on a diet of cream the excretion of phosphorus was also absolutely increased (the intake being equal).

The cause of this increased excretion of phosphorus in the urine, following the ingestion of milk-fat, must lie in the intestine. As previously remarked, owing to the formation of insoluble calcium soaps, the fat produces a change in the amount of calcium in the intestine, and this, again, sets free soluble phosphoric acid, which in its turn causes an improved absorption in the form of alkaline phosphates, especially ammonium phosphate. The result is the excretion of these in the urine.

Child M.: Two and a Half Months Old.

Amount of Urine in Twenty-four Hours.	*Nitrogen.*	P_2O_5.	*Ratio N : P.*	*Food.*
c.c.	Mgm.	Mgm.		
225	315·00	212·79	1·5	Cream.
260	364·00	242·43	1·5	
440	662·20	339·93	1·9	
376	500·08	297·80	1·7	
318	601·02	287·03	2·1	
500	735·00	306·36	2·4	
460	2543·80	545·32	4·7	Skim-milk.
460	2704·80	462·60	5·8	
530	2893·80	455·34	6·4	
395	2433·20	589·34	6·2	
585	2866·50	491·00	5·8	
570	2677·50	530·40	5·1	

[1] Quoted by Keller (160).

The amount of *organically combined phosphorus* in infants' urine has been estimated by Keller (163). Under very varying conditions, it amounts to 1·5 to 9·9 per cent. of the total phosphorus excretion. No particular influence could be ascribed to any special form of diet. A great part of the organically combined phosphorus, as has been shown by observations on fasting children, arises from broken-down body tissues and secretions. It has not been shown that this excretion is particularly high during digestive disturbances. Hence the *a priori* view that the organic phosphorus can act as an index of the oxidative power of the organism, and that its increase in the urine can be looked upon as showing a decreased oxidizing power.

The study of the *sulphur* compounds in infants' urine has been undertaken from a similar point of view. The question here to be decided was whether in children with gastro-intestinal diseases the excretion of neutral unoxidized sulphur was increased above normal, as a result of a decreased oxidizing power in the tissues of the child. Freund (164), who undertook this task, came to the conclusion that there was no increase in the sense stated above. He showed that, although the total sulphur excretion varied within wide limits, according to the amount of protein decomposition, the neutral sulphur remained constant within a narrow zone, and for the most part was independent of protein decomposition. The relative amount of neutral sulphur (in percentages of the total sulphur) is greater the less the protein ingested and the total sulphur excreted. For this reason, in Freund's experiments the amount of neutral sulphur was relatively and absolutely at its highest in healthy breast-fed children. Freund is willing to admit a double origin for the neutral sulphur. It appears in constant amounts as an isolated substance, not capable of further oxidation, but it is also an intermediate product of metabolism. This last portion explains the small variations of neutral sulphur always demonstrable in the portion derived from the food.

According to Freund's figures, the excretion of neutral sulphur cannot be taken as an index of more or less active oxidative function of the body, as in most children with gastro-intestinal disease—in which we have reason to suppose that there is a decrease in oxidizing power —a decrease was also found in the excretion of neutral sulphur (165). According to Freund, this may be due to an impaired secretion of bile.

Indican is not present in the urine of healthy breast-fed children [Senator (62), Zamfiresco (166), Hochsinger (167), Steffen (168)]. Momidlowski (74) and Concetti (169) found occasional traces in healthy children. In healthy artificially fed children it is not always present [Hochsinger, Gehlig (170)]. On the other hand, there is a constant relation between severe diseases of the intestine and increased indican excretion. Hochsinger observed an increased indican excretion in infective enteritis and in acute diarrhœa and vomiting. Momidlowski, Gehling, and Concetti also note increased indicanuria in cases of gastro-intestinal disease.

Bile pigment exhibits peculiar features. While bilirubin is practically always found in the urine in cases of adult jaundice, in the infantile form circumstances arise which prevent the appearance of the bile

pigments in the urine. At any rate, no bile pigments are excreted in the urine of children suffering from icterus neonatorum. Porak (171) in 198 cases only thrice found bilirubin in the urine, and Skormin (172) states that icterus neonatorum may be diagnosed by the failure of bilirubin to appear in the urine. On the other hand, in the urine of newborn jaundiced children, Parrot and Robin (173) found golden yellow, shining, insoluble masses of pigment—*masses jaunes*—soluble in alcohol, but not in ether, and dissolving in strong sulphuric acid with a red coloration [Cruse (174)]. The appearance of these masses of pigment points to the insolubility of bilirubin in urine. Knöpfelmacher (175) sought to explain this by pointing out that bilirubin was held in solution by alkaline salts, especially by the phosphates. But the amount of phosphates (especially the simple acid phosphates) is, according to Knöpfelmacher, so small in the urine of the newly-born, that an appreciable amount of bile pigment cannot be dissolved. But if for any cause there is sufficient phosphate present, the urine of icteric newly-born children will dissolve so much bile pigment that the positive staining reaction is lost. Cruse (174) and A. Epstein (176) have published such cases.

In some forms of infantile jaundice (septic) dissolved bile pigment is, according to Skormin, always found in the urine. Whether in these cases so much phosphate is present, owing to toxic protein decomposition, that a solution of bilirubin becomes possible must be determined later on.

The so-called catarrhal jaundice of infants does not differ as regards the excretion of bilirubin in the urine from that occurring in adults.

The occurrence of *acetone* in the urine of healthy and sick infants has as yet been little investigated. It is not yet known whether it is ever found in the urine of breast-fed children. In acute gastro-intestinal diseases Schrack (177) found acetone in the urine, but not in chronic nutritional disturbances. Schlossmann (14) found organic acids related to acetone (aceto-acetic acid, succinic acid, propionic acid, etc.) in gruel decomposed by *Bacillus coli communis*, and also acetone and butyric acid in the urine of children who were put on a " gruel " diet during illness. This caused him to draw a special clinical picture of an " intoxication " due to the decomposition of " gruel."

More recent researches by Langstein and Meyer (200) strip the excretion of acetone in acute gastro-intestinal disease in infants of its specific character. They show that it is not characteristic of any particular disease, and is merely the sequel of inanition, and the result of want of carbohydrate due to disturbances in carbohydrate metabolism. Excretion of acetone thus accompanies excretion of oxybutyric acid and an increase in the ammonia excreted in the urine.

Meyer (101) has made the excretion of *phenol* in the urine the object of his researches. It amounts (according to the Kossler-Penny-Neuberg method) to an average of 2·5 to 6 milligrammes per diem in breast-fed children, and 13·28 milligrammes in the artificially fed. Phenol ingested by the mouth is partly oxidized and partly deprived of its toxicity by synthesis into ethereal sulphates. A small amount is excreted as phenol. Infants with gastro-intestinal disease react in just the same way as healthy ones.

Sugar is not found in the urine of healthy infants [Parrot and Robin (178), Cruse (179), Grosz (131), and Koplik (180)], although reducing substances are occasionally present. On the other hand, as Grosz and Langstein and Steinitz have shown, lactosuria in infants is a frequent symptom of gastro-intestinal disturbances even of a trivial character. This lactosuria is alimentary. It disappears on a diet of water, and again appears when milk is given, as long as the metabolic disturbance lasts. It arises from an incomplete decomposition of the milk-sugar of the food in the bowel, whereby the milk-sugar reaches the circulation. In severe gastro-intestinal disturbances Langstein and Steinitz have also demonstrated galactose, a decomposition product of lactose, in the urine.

The question of the excretion of sugar in infants is closely connected with the question of its assimilation, and this depends on so many factors —the presence of inverting ferments in the intestine, rapidity of absorption, amount absorbed, and the bacterial processes in the bowel. The alimentary glycosuria of infants is a symptom which does not advance our knowledge of the meaning of intermediate metabolic processes. The facts which are proved beyond doubt [Grosz (131), Hecker (181), Nobécourt (182), Terrien (183), Keller (184)] permit the following conclusions: Milk-sugar is almost completely absorbed, more so than in adults. Glucose can also be ingested by the mouth in large quantities before it is excreted in the urine. On the other hand, lævulose in relatively small amounts produces alimentary glycosuria. Maltose is the best tolerated of all the varieties of sugar, even in infants with gastro-intestinal disease. The proportion of this sugar assimilated must be very high—so high that it was never recovered in Keller's experiments in spite of the large quantities administered. For example, in one case as much as 28·7 grammes maltose + 2·8 grammes lactose were given per kilogramme per diem without sugar being recognised in the urine.

In concluding the account of the changes in the urine under various metabolic conditions, we will shortly deal with two phenomena the relations of which in the physiology or pathology of metabolism have not yet been clearly established in spite of many investigations. These are *albuminuria* and the *uric acid infarct* of new-born infants. A complete collection of previous works and a detailed description of them will be found in the handbook by Czerny and Keller, to which we have referred for the literature. Here only the most important will be briefly collated.

In a large number of cases (40 to 100 per cent. of all new-born infants) we find albuminuria. The albumin is either already present in the first urine passed [Mensi], or appears two days later, and disappears in from five to ten days. A reason for this albuminuria has been sought in disturbances in the vital processes of the infant consequent on the change in metabolism, and the hyperæmia of the kidneys which results [Virchow]; in incomplete development of the glomeruli [Ribbert]; in uric acid infarction and consequent mechanical irritation of the kidney [Hofmeier], and, finally, in a chemical irritation of the kidneys by the very uratic urine of the first few days of life [Flensburg]. The protein occurring in this albuminuria was thought by Flensburg to be a nucleo-protein.

By the French authors [Parrot and Robin, Le Gendre, Cohen, Arnozan,

Perret, etc.] the albuminuria of the newly-born is almost always considered as pathological. There are even some authors [Perret], who consider the prognosis uncertain, because the kidneys are frequently damaged and less resistant to infection.

In near, but not quite clear, relationship to albuminuria stands the uric acid infarct of the newly-born. It arises from the fact that in the first few days of life a hyaloid substance is formed in the renal tubules, and upon this are deposited urates in considerable quantity. To pick out the theory as to the origin of this substance, which appears most probable (Flensburg's), the primary cause is the hyperleucocytosis of the first days of life, which causes an overproduction of uric acid. But why this is not excreted as such, but in the shape of an infarct (hyaline cylinders covered with uric acid and streaks and granules of urates), is not explained.

That in all cases the uric acid, which, according to Flensburg, is also to be regarded as an etiological factor of the albuminuria, plays a considerable part in the production of the infarcts is shown by the urinary analyses of Sjöqvist, from which we quote the following figures :

	In 100 *Parts of Urinary Nitrogen.*		
	Urea.	Uric Acid.	Ammonia.
1. Before the infarct	74·5	7·9	7·8
2. During the infarct	76·1	8·5	8·1
3. After the infarct	72·7	3·0	9·6

V.—THE METABOLISM OF ENERGY AND THE REQUIREMENTS OF NUTRITION.

Diet regarded as a source of energy, a view founded upon the law of the conservation of power, was first dealt with, as regards infant metabolism, by Camerer (185, 186). He expressed the food requirements of the infant in terms of heat units, and represented the metabolic equation in the form of a balance-sheet of energy ; that is to say, the potential energy taken into the body as food equals the work done by the body and that stored up within it. According to Camerer, if the energy spent on food, on the radiant heat, and on the evaporated water is termed c, the energy equal to outside work performed l, the energy represented by tissue increase a, that of the lost tissue substance k, then the position as regards the infant is $n(+k)=c+l+a$.

For the normal healthy infant the outside work is so small that it can be disregarded, and the equation becomes simplified to $n=c+a$; in other words, the energy in the food is converted into heat, a part of the energy being stored in the body as potential energy or growth.

If we wish to investigate completely the amount of energy used in metabolism, we must estimate the value of the food ingested in calories

(gross calories), and subtract from that the energy lost in the fæces. When from this (net calories) the calorie value of the urine and sweat is subtracted, we have a view of the energy actually used up, the energy which has passed through the body (physiological net effect).

Such investigations are at present but few in number; as far as we know, there are only the metabolism series of Heubner and Rubner, and an experiment by Cronheim and Müller (187).

If we compare the results of the oft-quoted experiments carried out by Rubner and Heubner, we arrive at the following figures:

Food.	*Daily Intake.*	*Loss in Urine and Fæces.*	*Net Physiological Value.*	*Calories per Diem per Kilogramme.*
	Calories.	Calories.	Per Cent.	Calories.
Normal child (human milk)	380·0	28·17	91·6	73·00
Normal child (cow's milk) ..	735·5	52·70	92·2	96·27
Marasmic child (cow's milk)	381·0	41·50	81·1	126·00
Marasmic child (malted meal)	301·2	37·30	82·4	66·00

Value per Diem for 1 Cubic Metre Superficies.

Food.	*Supply in Calories, subtracting Amount in Urine and Fæces.*	*Heat Production.*
		Calories.
Normal child (human milk)..	1,006	1,006
Normal child (cow's milk)	1,479	1,286
Marasmic child (cow's milk)	1,384	1,101
Marasmic child (malted meal)	428	1,076

The potential energy differs in the four experiments. The net physiological effect—that is, the available potential energy for the body—is in the experiment on the healthy child rather more than in the marasmic child, but only so slightly that the atrophic child, although on milk diet, got the largest number of calories per kilogramme per diem. Calculated per square metre of superficial area, the supply of energy varied between 1,479 and 428 calories.

As the heat production in the case of the breast-fed child, which maintained its body-weight during the experiment is exactly met by the potential energy, Rubner and Heubner assume that here we have a diet of equilibrium. On the assumption that this has a generally uniform value, the atrophic child on a diet of gruel, when putting on tissue, equally takes a diet of equilibrium, whilst on cow's milk the excess over and above a diet of equilibrium amounted to 44 per cent. in the healthy child, and 35·5 per cent. in the marasmic child.

A comparison of the metabolism of energy in healthy and marasmic children shows, therefore, the absence of any notable difference. No abnormal course of tissue or energy metabolism can be recognised in the metabolism of sick infants.

But, according to Heubner (188-190), there is a fundamental difference in the nutrition of the naturally and artificially fed child. Observations on normal thriving infants brought Heubner to the conclusion that, with the same supply of energy, more reserve of potential energy took place in the breast-fed than in the artificially fed child; in other words, that the latter, in order to store up as much as the former, must be supplied with a higher total intake. From this, and from the fact that artificially fed infants excrete more CO_2 than breast-fed, Heubner concluded that artificial food required more work for its digestion. The digestion of cow's milk requires more calories than that of human milk, and these calories leave the body as heat lost. If we express this relation by Camerer's terms, in the equation $n = c + a$, the factor c will in artificially nourished children be the greater. If it is large enough to equal n, growth is no longer possible; if it is still greater, the condition is that of commencing atrophy. This, according to Heubner, is owing to congenital incapacity of the intestinal canal or to acquired weakness of the epithelium, by which the work of digestion is abnormally difficult. The intestine is able to digest the food which is put into it, as is shown by good or passable absorption, but it requires so much energy for this process that not only is there none left for growth, but some of the tissue substance is used up.

A discussion of this theory can only, in our opinion, be possible when we measure the work done in digestion by infants, and this hitherto has not been accomplished.[1]

The consideration of diet from the standpoint of the doctrine of energy is not merely of theoretical interest, but has a distinct bearing upon practical treatment. By a comparison of the nutritive value of various food-stuffs, it enables us to calculate approximately the amount of nourishment ordinarily necessary. If we take the gross number of calories introduced with the food, of which the greater part will be absorbed by marasmic children, and divide this by the body-weight, we obtain the quotient of energy which, according to Heubner, shows (in calories) the food-intake per kilogramme per diem which is necessary for a child to put on weight in a satisfactory manner. Heubner puts the normal quotient of energy for the breast-fed child at 100, and for the artificially fed at 120 calories (his observations were few in number).

Without denying that the quotient of energy has advanced our method of thought, we shall now bring forward a few considerations which somewhat diminish its value as a means of calculating the requirements of nutrition.

In the first place, there are not at present enough observations to fix a definite normal quotient of energy. Even in the healthy breast-fed child the quotients hitherto published vary considerably,[2] and as

[1] Rubner and Heubner (203) experimented with a strong wet-nursed child by comparing the estimations of the energy equation. When the child was in a condition of hunger, and when it was fully fed, they hoped to arrive at the total energy used up in digestion. The experiment was spoiled only by the extreme restlessness of the child, which destroyed the value of the figures for the metabolism of a healthy hungry child. The most important result of this experiment lies rather in the numerical result as to the amount of energy lost in screaming and in other "work."

[2] The greater number are given by Czerny and Keller (2).

regards artificially fed children, the statistical material is still more sparse. Then, again, the determination of the quotient of energy is much too uncertain to serve as a basis for this kind of calculation. The calorie value of human milk, according to Heubner and Rubner (111), is 614·2 to 723·9; according to Gaus (149), 678·7 to 745; according to Reyher (190), 765; and according to Schlossmann (191), 702 to 863.

Lastly, it cannot be shown that the calorie value of milk, as determined directly by the calorimeter, exactly corresponds to that of the organic substances which it contains; and the calorie value of human milk, owing to the variations in its composition—especially in the amount of fat—cannot be determined with sufficient accuracy for a whole period of lactation, even by means of frequent analyses.

We cannot, therefore, estimate a dietary by its dynamic value. We know that it must contain a certain amount of protein, and no doubt, also, the amounts of fat and carbohydrate can be calculated to a certain extent. Beyond this the calorie requirements only give us the sum of the organic constituents, leaving us to calculate the amount of water and the proper quantity and quality of inorganic matter by an analysis of the food-stuffs.

These considerations are of still more importance when we wish to calculate the nutritive requirements of children with gastro-intestinal diseases by means of the quotient of energy. In these conditions, mistakes in diet upset nutrition sooner than in the healthy child, and, moreover, frequently there is a special intolerance of certain foods. A large number of children with gastro-intestinal disorders cannot take fat. They cannot, therefore, be adequately nourished by giving them a food of high calorie value such as cream. A child who has been made ill by an excess of carbohydrates requires very little carbohydrate in his food; one who has suffered from too much protein should have only the smallest quantities of protein. The therapeutic indications derived from the character of the diet which set up the illness loom so largely that the value of the quotient of energy is proportionally diminished. Good results from malt and butter-milk in dieting children with gastro-intestinal diseases are not solely due to the high calorie value of these foods, but because they are free from, or poor in, fat, and contain suitable carbohydrates. To similar causes are due the results of a full milk diet in certain cases of children who have been fed on cereal gruels.

VI.—ANOMALIES OF METABOLISM.

Disturbances of nutrition in infants may be divided into two classes—those which result from a general infection and those originating in the alimentary tract. We should *a priori* expect that these two classes, differing as they do both in their pathology and their clinical course, would have very different effects on metabolism.

Disturbances of metabolism of infective origin are not merely the result of infections of the gastro-intestinal tract; the clinical course of

other infections (pneumonia, otitis, erysipelas, tuberculosis, etc.) shows that here, too, a deleterious effect is produced on the metabolism of infants. The exact nature of this effect, and whether, or to what extent, it is the result of toxic disintegration products, is not yet determined. Schkarin's series of observations, however, on the metabolism of infants suffering from general infections show that in such cases there is no decreased power of absorption of food, but that, on the other hand, there is an interference with the retention of nitrogen, sulphur, and phosphorus in food, so that in severe cases the excretion may exceed the intake (191A). A diminished retention of calcium appears to be the rule in infective conditions.

Our definite knowledge of disturbances of metabolism in children suffering from gastro-intestinal diseases is confined to those resulting from improper feeding, the general characteristics of which depend on the way in which they originate. Some are caused by the action of one or more food-stuffs lasting for a considerable time. In these cases there arises a metabolic disturbance intrinsically trifling, which could easily be set right if the deleterious action were not too long-continued. In this way, little by little, is produced the condition known as chronic derangement of nutrition.

How far the excess or defect of any one class of food-stuff determines metabolic disturbances cannot be finally determined in the present state of our knowledge. In the case of some food-stuffs we only know from clinical observation that they have a deleterious influence on metabolism. Thus, we know that excess of protein is not unimportant in infant feeding, although Keller's (118) metabolism experiments showed no recognisable ill-effect from excessive amounts. Equally bad results follow if the infant's diet contains too little protein ; at least, it appears that a long-continued diet of vegetables without milk (water-gruels), besides other ill-effects, causes the gravest and most irreparable damage to nutrition, owing to the fact that the child is given too small an amount of protein, and that in the least easily assimilable form [Heubner and Rubner].

How far excess or defect of the inorganic constituents of diet and water influence metabolism cannot be clearly determined by clinical observation.

The ill-effects produced by long-continued excess of fat on the infant's constitution have been more completely studied. These are in close relationship with the question of "acidosis," inasmuch as most cases of the latter condition are induced by an excess of fat in the diet. We shall, therefore, first deal with what is known about acidosis in infants, and then go on to describe the effects upon the organism.

If we consider how an acidosis, or an increased acidity of the organism, can be produced, two alternatives appear possible—namely, an increased production of acid (absolute acidosis), or a decrease in the amount of alkali present (relative acidosis). In either case an increased excretion of ammonia by the kidneys results. In increased acid production the acids combined first with the fixed alkalis, but as these are generally

insufficient, an increased ammonia excretion follows. In the second alternative, since the organism is endeavouring to spare its store of alkali, it follows that the increased ammonia excretion in the urine is primary. The behaviour of the ammonia and the fixed alkalis in the two conditions is therefore as follows :

	Excretion in Urine.	
	Absolute Acidosis.	Relative Acidosis.
Fixed alkali	Increased	Decreased
NH_3	Increased	Increased

In order to determine which sort of acidosis is present, the principal point is to know its place of origin. When acids are either absorbed from the intestine or formed out of intermediary metabolic products, there is an absolute acidosis (diabetes mellitus, experimental acid-intoxication) ; but if acids, while still in the intestine, are neutralized by alkalis taken in food or obtained from the tissues, or if the fixed alkalis are withdrawn from the body in some other way—*e.g.*, in diarrhœa—a relative acidosis results.

We have now to determine to which class the acidosis associated with nutritional disturbances in children belongs.

Researches on acidosis in children suffering from gastro-intestinal diseases take origin in the fact, first established by Keller, that in such cases the ammonia excretion in the urine is either delayed or disappears.

Few researches on the excretion of ammonia by healthy children during the first year of life are available. Sjöqvist (192) found in newborn infants and in children of all ages that the ammonia coefficient[1] was 7·8 to 9·6 per cent. There are few observations on the ammonia excretion in healthy, well-nourished breast-fed infants ; most of the published material relates to those who are ill. The few figures given by Pfaundler (153) vary from 6·4 to 15·3 per cent. A six-months old child observed by Camerer (156) excreted 8 per cent. NH_3. In a healthy bottle-fed child Camerer found the nitrogen coefficient to be 5 per cent.

Keller only observed children with gastro-intestinal complaints. In these he almost invariably found an abnormally high ammonia excretion amounting to 52 per cent. of the total nitrogen. This was either continuously present, or recurred from time to time. In attempting to explain this fact, the question arises whether the rise in ammonia excretion is not merely the result of disturbed urea production in the liver, and not due at all to an acidosis. This view gains some support from

[1] The ammonia coefficient is the amount of ammonia nitrogen : the total nitrogen.

the latest histological investigations of Thiernich (193), Terrien (205), Lesné and Merklen (206), and others, from which it appears that degeneration of the liver cells occurs in children with gastro-intestinal disease. Van der Bergh (194) instituted experiments to elucidate this question. Starting from the supposition that the increased ammonia excretion from the kidneys resulting from acidosis must be referred to an increased utilization of the fixed alkalis, and that, consequently, a decreased synthesis of urea would be uninfluenced by the exhibition of fixed alkalis, Van der Bergh gave sodium bicarbonate to infants suffering from digestive disturbances. The result was that the ammonia excretion immediately disappeared, either partially or completely. In another series of observations, Keller (120) demonstrated an increase in urea excretion corresponding to the decreased ammonia output. Moreover, Keller (53) endeavoured to show that such infants had the power of forming urea by feeding them with ammonium carbonate ($\frac{3}{4}$ to 1 gramme — 10 to 15 grains). If the power of producing urea were damaged, the exhibition of ammonium salts should produce an increase of ammonia in the blood, and a consequent increase in the amount excreted by the kidneys. This, however, did not occur, but the urea excretion went up under the influence of the ammonium carbonate, showing that the power of forcing urea was intact. In the same way amido-acids (leucin, glycocoll, asparagin), given *per os*, were for the most part converted into urea in children suffering from gastro-intestinal disorders (195).

Pfaundler (153) disputes the view that the formation of urea remains intact. His investigations led him to think that increased ammonia excretion in a proportion of children with digestive diseases—namely, those in which a degeneration of the liver cells is present—is the result of increased ammonia production, which must be referred to an imperfect urea synthesis. He noted that in such cases the power of the liver to oxidize salicylic aldehyde to salicylic acid post-mortem was very much diminished. But the fact that after death the liver cells have a diminished oxidation power for salicylic aldehyde, taken together with the degenerative appearances in the cells, is not sufficient to establish a decreased power of synthesizing urea during life.

Van der Bergh's and Keller's researches already mentioned, the accuracy of which Pfaundler could not dispute, and the analogy with adults in whom the formation of urea, even in the most severe diseases of the liver, is usually unaffected [Weintraud, Münzer], compel us to regard the increased excretion of ammonia in the urine of children with digestive disturbances as an indicator and neutralizer of acids, and not as a result of defective formation of urea.

According to Keller, in children with chronic gastro-intestinal affections an increase of ammonia excretion nearly always takes place, and Kolsky (196) observes that this is generally dependent on the condition of the child. The further question now arises as to whether diet influences the ammonia excretion, and which of the food-stuffs produce an increased ammonia output during the process of metabolism. The answer to this question is supplied by a research of A. Czerny and A. Keller, which indisputably shows that of all the food-stuffs, fat is the only one

which leads to an increased output of ammonia. The following figures are selected from these investigations :—

	Amount of Urine.	*Total Nitrogen.*	*Ammonia Nitrogen.*		*Food Content.*		*Diet.*
			Amount.	Total Nitrogen.	Protein.	Fat.	
CASE II. (2 MONTHS) :	c.c.	Mgm.	Mgm.	Per Cent.	Per Cent.	Per Cent.	
March 25	460	2543·80	128·80	5·10	3·40	0·10	Skim milk.
„ 28	460	2704·80	83·72	3·10	3·40	0·10	
„ 30	530	2893·80	44·52	1·50	3·40	0·10	
„ 31	395	2433·20	44·24	1·80	3·40	0·10	
April 2	385	2866·50	65·52	2·30	3·40	0·10	
„ 3	510	2677·50	55·08	2·70	3·40	0·10	
March 3	225	315·00	53·55	17·0	0·86	3·60	Cream.
„ 6	260	364·00	87·36	24·0	0·86	3·60	
„ 10	440	662·20	104·72	15·8	0·86	3·60	
„ 13	376	500·08	168·45	33·7	0·90	5·70	
„ 17	318	601·02	133·56	22·3	0·90	5·70	
„ 21	500	735·00	131·00	15·0	0·90	5·70	
April 9	550	654·50	100·10	15·2	0·90	5·90	Cream.
„ 10	515	721·00	108·15	15·0	0·90	5·90	
„ 11	430	421·40	84·28	20·0	0·90	5·90	
„ 13	420	441·00	70·56	16·1	0·90	5·90	
CASE V. (8 MONTHS) :							Skim milk with 25 grm. milk-sugar daily.
May 28	755	1744·10	13·42	3·6	1·10	0·03	
„ 29	730	1576·75	59·36	3·7	1·10	0·03	
„ 30	630	2063·70	52·78	2·5	1·10	0·03	
CASE VI. (2 MONTHS) :							
May 28	465	830·00	26·04	3·1	1·10	0·03	
„ 29	515	594·80	25·24	4·2	1·10	0·03	
„ 30	505	642·80	21·70	3·4	1·10	0·03	

There are thus, according to Keller (154), two factors which influence the excretion of ammonia—(1) the fat-content of the food, and (2) the condition of the child. He found, indeed, that even when the amount of fat in the diet was low, there was in many cases an increased ammonia excretion. Keller's (118) experiments, undertaken in order to obtain a measure of the acidosis from the estimation of the acidity of the urine in children with gastro-intestinal diseases, deserve mention. Estimations of the acidity (after Lieblein) of the urine from children on diets both rich and poor in fat did not indicate any constant ratio. The acidity appeared quite irregular, and was not always high in cases where acidosis might be expected. From this it appears that an excretion of free acid does not take place in the urine in gastro-intestinal diseases, but that there is always enough ammonia available to neutralize them before they are eliminated.

Keller's work was dominated by the view that the acidosis, and with it the increased ammonia elimination, was due to the abnormal absorption and assimilation of acids presumably originating in the intestine. But by degrees a change of opinion has taken place in the conception

of acidosis, which has thrown the idea of " absolute acidosis " into the background. Keller (120) had suggested what Steinitz (138) has now shown—namely, that alkalis are excreted into the intestine, and in view of this the acidosis must be regarded as " relative " (see p. 881). It is conclusively shown that the increase in ammonia excretion caused by a diet rich in cream can be explained by the excretion of fixed alkalis through the intestine. The increased excretion of phosphorus, which has also been shown to occur under like circumstances, also increases the acidity of the organism.

Whether abnormal unoxidized organic acids appear as intermediate products of metabolism, or in the urine, and increase the acidosis, is not clear. Keller was unable to discover any such acids, and their existence is not *a priori* an obvious necessity, as it seems certain that the tissues of children with gastro-intestinal diseases have a diminished oxidizing power. At any rate, Pfaundler found the oxidation power of the liver for salicylic aldehyde diminished post-mortem. Freund (165) found an unusually small excretion of phenol after the administration of benzol to children. In any case, the diminished power of oxidizing phenol, or salicylic aldehyde, does not indicate a general loss of oxidizing power in the organism as a whole, and the results obtained by Freund, showing that in children with gastro-intestinal disease there is no increase in the proportion of neutral sulphur compared with the organic phosphorus compounds, does not support the view that the metabolic disturbances cause any decrease in general oxidizing power.

To sum up shortly our knowledge of the course and significance of acidosis in children suffering from chronic gastro-intestinal disease, the condition is one of relative acidosis, the result of which is the increased excretion of ammonia by the kidney. The primary event is the increased excretion of alkalis by the intestine, brought about by the fat taken as food, which contributes to the abnormal processes in the gut in so far as it increases alkali excretion. The alkalis are got rid of either unchanged or as soaps ; but besides this, they also serve to neutralize the increased phosphoric acid, the cause of which is the simultaneous increase in the amount of calcium phosphate combining with fat to form a calcium soap.

The importance of relative acidosis in chronic disturbances of nutrition in infants lies in the loss of alkali. For the growth and health of the child's organism the retention of alkali is as important as the retention of nitrogen, phosphorus, or other mineral substances. If it is withheld, or a loss takes place, the condition of the body can neither improve nor remain normal. Under these circumstances, owing to the endeavour of the body to keep its relative composition unchanged, failure to increase in weight or loss of tissue substance occurs ; and since growth in height can take place even when the body-weight is not increasing, or is actually decreasing, eventually the case presents the clinical features of an atrophy which is alimentary in origin.

The theory we have set forth of the origin of atrophic conditions in infants on an alimentary basis corresponds accurately with clinical experience. We see atrophic conditions occurring without any previous

toxic or infective illness; merely through unsuitable diet, with excess of fat, the children become atrophic. Neither diarrhœa, nor vomiting, nor general symptoms of any kind, need enter into the symptom-complex, and yet, with a sufficient supply of calories and complete nitrogen assimilation, the weight remains the same during long periods, or even decreases to an extreme degree when a secondary infection often ensues and masks the clinical picture. Moreover, this theory of the causation of atrophy gains support from the results obtained by a definite therapeutic system. Feeding with gruels and butter-milk owes its excellent results only to the fact that these foods are poor in fat, and that the loss in calorie value due to fat deficiency is made up for by sufficient amounts of easily assimilated carbohydrate. Morse (212) did not find acetone or diacetic acid in infants under two years of age who were kept for twenty-eight hours without food for therapeutic purposes, nor in fifteen infants who had been partially starved for considerable periods. It is remarkable that in these latter cases the food given always contained a considerable amount of carbohydrate. Rothschild (213) has described 300 cases of fat dyspepsia in infants, some of whom were breast-fed. The condition is one of chronic entero-colitis. Vomiting and characteristic stools are usually present. The treatment by butter-milk is satisfactory.

The deleterious influence of fat on infant metabolism has also been recently determined by other considerations. Salge (97), from clinical observations, came to the conclusion that in a great number of infants with gastro-intestinal disturbances fat, even that of human milk, could not be tolerated. The theoretical basis for this was, however, arrived at from another point of view. He thought that certain bacteria, which specially influenced the fat metabolism of infants, played a part in the etiology of digestive disturbances, especially in acute catarrhal enteritis. In catarrhal enteritis, which is characterized clinically by the passage of frequent acid, watery stools, and a number of severe nervous symptoms (toxic), Salge found the *Bacillus acidophilus* of Finkelstein and Moro invariably present in the motions. This bacillus only differs very slightly from the ordinary "blue" bacillus found in stools of normal breast-fed children. According to Salge, this bacillus grows better on a fatty medium than on ordinary broth. For instance, there was luxuriant growth on a medium containing sodium oleate, which substance was decomposed, lower fatty acids—propionic, butyric, acetic, and formic—being produced. Toxic symptoms were produced both by the bacillus and by an extract from their bodies. Salge was of opinion that the fat taken in food primarily induced abnormal bacterial decomposition by means of the *B. acidophilus*, and that the products of this decomposition at once irritated and inflamed the gut, and, owing to their acid character, drew off the fixed alkali from the system.

Without denying Salge's results, we would briefly point out that it does not appear to us possible to apply results obtained *in vitro* directly to the living organism. For though, after inoculating a broth mixed with the salt of a fatty acid with *B. acidophilus*, and allowing this to stand for some days, a decomposition of the fat into lower fatty acids

may eventually occur, we have no right to assume that the same process goes on in the living organism.[1]

Moreover, we cannot regard as above criticism Salge's (199) clinical reports from which he deduces the acute deleterious influence of fat on the general health. At least, the clinical histories do not show with certainty that it is the fat in the mother's milk which produces the deterioration in the children's condition.

That acidosis is present in children suffering from catarrhal enteritis is established by researches less open to objection. Langstein and Meyer (200) found that the fæces in these acute cases contained considerably more volatile fatty acids than those of normal or chronically sick infants. The fæces passed in twenty-four hours by healthy infants had an acidity equal to 30 c.c. $\frac{N}{10}$ NaOH at most; the same from infants with catarrhal enteritis reached 100 c.c. $\frac{N}{10}$ NaOH.

An excretion of alkali, due to the increase of fatty acids in the stools, also appears in infants with acute nutritional disturbances, as in the chronic conditions. But here two other factors appear which alter metabolism—namely, hunger and a disturbance of the carbohydrate metabolism.

This disturbance, which finds its expression in the excretion in the urine of lactose and galactose [Langstein and Steinitz], and the feeling of hunger, compel the child with catarrhal enteritis temporarily to satisfy his calorie wants with protein and fat alone. This causes an intermediary acidosis, which in its turn sets up an increased excretion of ammonia and acetone in the urine.

A diet of gruels alone, in contradistinction to that just described, is characterized by producing its bad effects, not through an excess of one dietetic principle, but through deficiency of those substances which are important to health. We have already pointed out that the ordinary liquid gruels which are often given to infants for weeks or months, without the addition of milk, contain extremely little nitrogen. Keller (204) calculated the proportion of nitrogen in gruel made from flour as 0·06 per cent. His metabolism experiments further showed that children fed on gruel excreted a much greater amount of nitrogen in the stools, and failed to maintain their nitrogenous equilibrium. A diet of gruel thus carries with it the danger of deficiency of nitrogen, but this danger, as Keller shows, is not the only one. Simple gruels all contain so little chlorine and sodium that they cannot under any conditions satisfy the needs of the infant organism for these substances. As also mothers—at least, in this country—usually omit to add salt to gruel, a chlorine hunger is added to the nitrogen hunger, and this, according to Keller, may reach such a degree that the excretion of chlorides by the urine is

[1] Compare the similar objection to the test-tube experiments of Schlossmann (14), which Heubner (129) raised with regard to the discussion on the absorbability of gruel.

completely arrested. Both these processes—want of protein and want of chlorides—easily produce disturbances of metabolism which can be distinguished from other gastro-intestinal affections both by their clinical symptoms and by the ease with which they yield to treatment.

Another example of abnormal metabolism which is almost exclusively observed in children between the ages of six and twenty-four months is the so-called Barlow's disease, which must be reckoned as one form of scorbutus. This is considered a metabolic disorder, as its onset is induced by the nature of the food, and cure can be effected by a change in diet. No researches exist which throw any light on the pathogenesis of Barlow's disease. All the observations recorded in the literature deal with the determination of the kind of diet which produces scorbutus and that by which it may be cured. Hutchison (214), in an attempt to throw further light on the etiology of the condition, dialyzed fruit-juice, and gave the crystalline and colloid portions separately to children suffering from infantile scurvy. He found that the crystalline constituents alone had not any therapeutic influence. But the administration of potassium tartrate, citrate, and malate (the chief salts occurring in fruit-juice) in considerable doses has but slight action in arresting the disease. *A priori* he considers that the citrates are probably the salts chiefly concerned. On boiling the more soluble amorphous calcium citrate in milk, it separates out in crystalline form. However, calcium citrate has even less therapeutic value than potassium citrate. Hutchison has shown that there is no reduction in the coagulability of the blood in infantile scurvy. He quotes Sir A. E. Wright, who has examined the blood as to its alkalinity both in infantile scurvy and in cases in adults, and in both found a diminution of alkalinity. The cereal foods yield a more acid ash than does milk.

Experience shows that Barlow's disease is almost entirely limited to artificially fed children, but it is observed with very varied kinds of diet. All the cases, however, have the common characteristic that for a long period the same food has been used, and that a "denaturalized" one. The correctness of the supposition that though denaturalization changes are produced in the food which set up scorbutus, is shown by the fact that a change to fresh, raw, or only slightly boiled milk and fresh vegetables brings the symptoms to an end. The denaturalization of the food cannot alone be regarded as the cause of scorbutus, as only an infinitesimal proportion of the children who are fed on denaturalized food get scorbutus. We can only assume that there is some special liability to the disease.

It follows from our remarks that there are still many questions on the subject of the metabolism of children which await elucidation. The results set forth already are constantly showing how disturbances of metabolism may be approached by means of exact research. Only

when our knowledge of the nature of the various metabolic anomalies caused by fat, protein, carbohydrate, water, and salts, is large enough to enable us in each individual case to completely analyze all the symptoms will the time come to turn our eyes on the goal of modern pædiatrics —namely, the construction of a system of diet for health and disease based on scientific principles.

LITERATURE.

1. Camerer: Die künstl. Ernährung der Säuglinge. Ar. K. **2.** 447.
2. Czerny u. Keller: Des Kindes Ernährung, Ernährungsstörungen und Ernährungstherapie. P. 85.
3. Camerer u. Söldner: Die chem. Zusammensetz. des Neugeborenen. Z. B. **39.** 173. **40.** 529. **43.** 1.—Die Aschenbestandteile des neugeborenen Menschen und der Frauenmilch. Z. B. **44.** 61.
4. Ohlmüller: Ueber die Abnahme der einzelnen Organe bei an Atrophie gestorbenen Kindern. Z. B. **18.** 78. 1882.
5. Sommerfeld: Zur Kenntnis der chem. Zusammensetz. des kindl. Körpers im ersten Lebensjahre. Ar. K. **30.** 253.
6. Steinitz: Ueber den Einfl. von Ernährungsstörungen auf die chem. Zusammensetz. des Säuglingskörpers. Ja. K. **59.** 447.
6a. Steinitz u. Weigert: Ueber den Einfl. einseitiger Ernährung mit Kohlenhydr. auf die chem. Zusammensetz. des Säuglingskörpers. Be. P. P. **6.** 206.
7. Schlossmann u. Moro: Die Ernähr. des Erwachsenen mit Kuh- und mit Frauenmilch. Z. B. **45.** 261.
8. Bunge: Ueber die Aufnahme des Eisens in den Organismus des Säuglings. Z. p. C. **13.** 399.—Über die Aufnahme des Eisens in den Organismus des Säuglings. Z. p. C. **16.** 173. **17.** 63.
9. Philippson: Ueber den Eisengeh. der Leberzellen bei Neugeborenen und Kindern im ersten Lebensjahre. Diss. Breslau, 1904.
10. Ritter v. Rittershain: Das Mundsekret der Neugeborenen und jüngeren Säuglinge. Jahrb. f. Phys. u. Path. d. Kindes. **1868.** P. 131.
11. Schiffer: Ueber die saccharifizierenden Eigenschaften des kindl. Speichels. B. k. W. **1872.** Nr. 29.
12. Korowin: Über Assimilation der stärkehalt. Speise bei Säuglingen. Ja. K. **8.** (N.F.) 380.
13. Zweifel: Über den Verdauungsapparat von Neugeborenen. 1874.
14. Schlossmann: Ueber die mutmassl. Schicksale des Mehles im Darme junger Säuglinge. Ja. K. **47.** 116.
15. Schilling: Zur Sekretion der Speicheldrüsen, insbesondere der Gland. submaxillaris, im Säuglingsalter. Ja. K. **58.** 518.
16. Epstein: Ueber Magenausspülungen bei Säuglingen. Ar. K. **4.** 325.
17. Jager: Die Verdauung und Assimil. des gesunden und kranken Säuglings nebst einer ration. Methode zur Säuglingsernährung. 1898.
18. Labbé: Du chimisme gast. normal chez les nourissons. R. M. E. **15.** 401.
19. Sotow: Bestimmung der Salzsäure nach der Methode von Hayem und Winter im Magen von Säuglingen. Diss. St. Petersb., 1893.
20. Escherich: Die normale Milchverdauung des Säuglings. Ja. K. **27.** 100.
21. Troitzky: Die Verdauung im Magen bei kleinen Kindern und die ther. Bedeut. der Ausspülungen desselben. Ja. K. **32.** 339.
22. Moncorvo: Sur les troubles dyspep. dans l'enf. et sur leur diag. par la recherche clin. du sac gastrique. 1889.
23. Bauer u. Deutsch: Das Verhalt. der Magensäure, Motilität und Resorp. bei Säuglingen und Kind. unter phys. u. path. Verhält. Ja. K. **48.** 22.
24. Cassel: Zur Kennt. der Magenverdauung bei Atrophia infantum. Ar. K. **12.** 175.
25. Thiercelin: De l'infection gastrointest. chez l'enfant nouveau-né. Thèse de Paris. 1894.
26. Wohlmann: Ueber die Salzsäureprod. des Säuglingsmagens im gesunden und kranken Zustande. Ja. K. **32.** 297.

27. Van Puteren: Ueber die Phys. der Magenverdauung bei Brustkindern. Diss. St. Petersb., 1889.
28. Leo: Ueber die Funktion des norm. und kranken Magens und die ther. Erfolge der Magenausspülung im Säuglingsalter. B. k. W. **1888.** Nr. 49.
29. Cohn: Gibt es eine Hyperchlorhydrie im Säuglingsalter? Diss. Breslau, 1898.
30. Clopatt: Contrib. à l'étude du chimisme stomacal chez les nourissons. Re. m. **12.** 249.
31. Einhorn: Cit. after Lit. Nr. 33.
32. Heubner: Ueber das Verhalt. der Säuren während der Magenverdauung des Säuglings. Ja. K. **32.** 27.
33. Hecker: Ueber die Funktionen des kindl. Magens bei Verdauungskrankh. Ja. K. **56.** 657.
34. Wolf u. Friedjung: Zur Würdigung der Magenverdauung im Säuglingsalter. Ar. K. **25.** 161.
35. Meyer: Zur Kennt. der Magensaftsekr. der Säuglinge. Ar. K. **35.** 79.
36. Oddo et de Luna: L'hyperchlorhydrie au premier âge. S. m. H. **1896.**
37. Knöpfelmacher: Hyperchlorhydrie im Säuglingsalter. W. k. W. **1900.** 1188.
38. Freund: Ueber Pylorusstenose im Säuglingsalter. G. M. C. **11.** 300.
39. Escherich: Pathogen. der bakter. Magen- und Darmerkrank. im Säuglingsalter. V. G. K. **1889.** 106.
40. Müller: Zur Kennt. des Verhalt. von Milch und Kasein zur Salzsäure. Ja. K. **34.** 439.
41. Hamburger: Ueber die Wirk. des Magensaftes auf pathogene Bakterien C. k. m. **11.** 425. 1890.
42. Langermann: Über den Bakteriengeh. von auf verschiedene Art und Weise zur Kinderernähr. sterilisierter und verschiedentlich aufbewahrter Nahrung, zugleich mit den Ergebnissen über ihr Verhalten im Magen selbst. Ja. K. **35.** 88.
43. Czerny: Die Ernähr. des Säuglings auf Grundlage der physiol. Funktionen seines Magens. P. W. **1893.** 495.
44. Wachsmuth: Ueber die "Schwerverdaulichkeit" der Kuhmilch im Säuglingsalter. Ja. K. **41.** 174.
45. Toch: Ueber Peptonbild. im Säuglingsmagen. Ar. K. **16.** 1.
46. Szydlowsky: Kenntnis des Labenzyms nach Beobacht. an Säuglingen. Ja. K. **34.** 411.
47. Escherich: Beitr. zur Frage der kindlichen Ernährung. Ja. K. **32.** 232.
48. Okouneff: Die Bedeut. des Labfermentes (des Chymosins) bei den Assimilationsproz. des Organismus. W. **1895.** Ma. **25.** 291.
49. Sawjalow: Zur Theorie der Eiweissverdauung. Ar. P. M. **85.** 171.
50. Rotondi: Ueber die Verdauungswirk. des Labfermentes. Mo. K. **2.** 595.
51. Hammarsten: Lehrb. für phys. Chemie. 3rd Ed. P. 383. (Also English translation.)
52. v. Dungern: Eine prak. Methode, um Kuhmilch leichter verdaulich zu machen. Mu. m. W. **1900.** 1661. Further literature in Oppler: Ueber Säuglingsernähr. mit gelabter Vollmilch. Diss. Breslau, 1903.
53. Keller: Gastroenteritis im Säuglingsalter. Ja. K. **47.** 187.
53a. Jacubowitsch: Von den quantitat. Bestandteilen der Galle bei den Neugeborenen und Säuglingskindern. Ja. K. **24.** 373.
53b. Baginsky u. Sommerfeld: Zur Chemie der kindlichen Galle. Ar. K. **19.** 321.
54. Moro: Über diastat. Enzym in den Stühlen von Säuglingen und in der Muttermilch. Ja. K. **47.** 342.
55. Gillet: Des troubles de la sécrétion pancréat. chez les enfants. Ja. K. **33.** 222.
56. Jacubowitsch: Zu der Lehre über die Funktion der Verdauungsfermente bei Kindern bei verschied. Erkrankungen. Ja. K. **47.** 195.
57. Gregor: Der Fettgeh. der Frauenmilch und die Bedeutung der phys. Schwankungen desselben in Bezug auf das Gedeihen der Kinder. Vo. s. V. **1901.** Nr. 302.
57a. Reyher: Ueber den Fettgehalt der Frauenmilch. Ja. K. **63.** 601.

57B. Engel: Zur Methodik der Fettbestim. in der Frauenmilch. Ar. K. **43** 181.
58. Blauberg: Exper. und krit. Studien über Säuglingsfäzes. 1897.
59. Hellström: Über Veränderungen in der Bakterienzahl der Fäzes bei Neugeborenen. Ar. Gy. **63** Hft. 3. 1901.
60. Langstein: Über die Azidität und den Zuckergeh. von Säuglingsstühlen. Ja. K. **56** 350.
61. Hedenius: Ueber das Schicksal der Kohlehydrate im Säuglingsdarm. Ar. V. **8.** 379.
62. Senator: Ueber das Vorkommen von Produkten der Darmfäulnis bei Neugeborenen. Z. p. C. **4.** 1.
63. Winternitz: Ueber das Verhalt. der Milch und ihrer wichtigsten Bestandteile bei der Fäulnis. Z. p. C. **16.** 460.
64. Hirschler: Ueber den Einfl. der Kohlehydr. und einiger anderer Körper der Fettsäurereihe auf die Eiweissfäulnis. Z. p. C. **10.** 306.
65. Rovighi: Die Aetherschwefelsäuren im Harn und die Darmdesinfektion. Z. p. C. **16.** 20.
66. Schmitz: Die Eiweissfäulnis im Darm unter dem Einfl. der Milch, des Kefyrs und des Käses. Z. p. C. **19.** 378.
67. Eisenstadt: Ueber die Möglichkeit, die Darmfäulnis zu beeinflussen. Diss. Berlin, 1897.
68. Bienstock: Ueber die Milchfäulnis. Verhinderung der Fäulnis durch Milch. Ar. Hy. **39.** 390.
69. Escherich: Darmbakterien. 1886.
70. Biedert: Ueber normale Milchverdauung. Ja. K. **28.** 344.
71. Biedert: Kinderernährung im Säuglingsalter. 1900.
72. Moro: Über die Darmbakterien des Säuglings. Ja. K. **61.** 687.
73. Baginsky: Ueber Cholera infantum. Ar. K. **12.** 1.
74. Momidlowski: Ueber das Verhalt. des Indikans bei Kindern. Ja. K. **36.** 192.
75. Kast: Ueber die quant. Bemessung der antisept. Leistungen des Magensaftes. Feststchr. zur Eröffnung des N. A. K. Hamburg, 1889.
76. Stadelmann: Einfl. der Alkalien auf den menschl. Stoffwech. 1890.
77. Biernacki: Ueber die Darmfäulnis bei Nierenentzündung und Ikterus nebst Bemerkungen ü. d. norm. Darmfäulnis. D. Ar. M. **49.** 87.
78. Mester: Ueber Magensaft und Darmfäulnis. Habilitationsschr. Breslau, 1893.
79. Schmitz: Die Beziehung der Salzsäure des Magensaftes zur Darmfäulnis. Z. p. C. **19.** 401.
80. Wasbutzki: Ueber den Einfl. von Magengärungen auf die Fäulnisvorgänge im Darmkanal. E. A. **26.** 133.
81. Schmidt: Ueber Funktionsprüfung des Darmes und über die diag. Bedeut. der Fäzesgärungen. K. i. M. **16.** 571.
82. Widerhofer: Die Krankh. des Magens und Darmes. Gerhardt's Handb. d. Kinderkh. **4.** 2.
83. Escherich: Die Bedeut. der Bakterien in der Aetiol. der Magen-Darmerkrankungen der Säuglinge. V. G. K. **1898.** 1.
84. Raczynski: Dyspepsia intest. acida lactatorum. W. k. W. **1903.** 342.
85. Escherich: Beitr. zur antisep. Behandlungsmethode der Magen-Darmkrankh. des Säuglingsalters. Ja. K. **27.** 126.
86. Pusch: Ueber die Gärungsverhält. und den Eiweissgeh. der Fäzes gesunder und kranker Kinder im ersten Lebensjahre. Diss. Bonn, 1898.
87. Callomon: Über das Verhalt. der Fäzesgärung bei Säuglingen. Ja. K. **50.** 369.
88. Pfeiffer: Ueber die Verdauung im Säuglingsalter bei krankhaften Zuständen. Ja. K. **28.** 164.
88A. Wernstedt: Ueber ein oxydierendes Ferment als eine Veranlassung des Auftretens grüngefärbter Stühle im Säuglingsalter. Mo. K. **4.** 241.
89. Schmidt: Ueber Hydrobilirubinbild. im Organismus unter normalen Verhältnissen. K. i. M. **13.** 320.
90. Schikora: Zur Kenntnis der Gallenfarbst. in den Fäzes der Säuglinge. Diss. Breslau, 1901.
91. Langstein: Ein Beitr. zur Kenntnis des weissen Säuglingsstuhles. Festsch. f. Salkowski. 1904.

92. Neubauer: Cit. after Lit. Nr. 91.
93. Quest: Über Darmgase bei Säuglingen mit Tympanites. Ja. K. **59.** 293.
94. Leo: Ueber Tympanites im Säuglingsalter. V. G. K. **1899.** 184.
95. Czerny: Gastroenteritis im Säuglingsalter. Intoxikation. Ja. K. **44.** 15.
96. Lesage: S. m. H. **1898.** R. M. E. **17.** 69.
97. Salge: Bakteriol. des Enterokatarrhs. Ja. K. **59.** 399.
98. Köppen: Milchgift und -Vergiftung. Ja. K. **47.** 372.
99. Finkelstein u. Ballin: Die Waisensäuglinge Berlins und ihre Verpflegung im städt. Kinderasyl. 1904. P. 32.
100. Spillmann: Le Rachitisme. 1900. P. 242.
101. Durante: Virulenza della Flora batterica intestin. e tossicità fecale nella enteriti infantili. Ped. **10.** 169.
102. Schütz: Zur Kennt. der natürl. Immunität des Kindes im ersten Lebensjahre. Ja. K. **61.** 122.—Schütz: Orvosi Ujság. **1904.** Nr. 3.
103. v. Zaremba: Über die entgiftende Funktion des Pankreas. Ar. V. **6.** 403.
104. Behring: Tuberkulosebekämpfung. B. k. W. **1903.** Nr. 11.—Beitr. zur exper. Ther. H. 8. 1904.
105. Römer: Über die intrauterine und extrauterine Antitoxinübertragung von der Mutter auf ihre Deszendenten. B. k. W. **1901.** Nr. 46.
105a. Ganghofner u. Langer: Ueber die Resorp. genuiner Eiweisskörper im Magendarmkanal neugeborener Tiere und Säuglinge. Mü. m. W. **1904.** Nr. 34.
105b. Uffenheimer: Über die Durchgängigkeit der Wandungen des Magendarmkanals neugeborener Tiere für Bakterien und genuine Eiweiss-stoffe. Ar. Hy. **1906.**
106. Salge: Ueber den Durchtritt von Antitoxin durch die Darmwand des menschl. Säuglings. Ja. K. **60.** 1.
106a. Hamburger u. Speck: Eiweissresorption vom Darm aus. W. k. W. **1904.** Nr. 23.
107. Tschernoff: Über Trockensubstanz des Kotes auf seinen Gehalt an Stickstoff und dessen Schwankungen in den Exkrementen im Zusammenhang mit der Nahrung und den verschiedenen Krankheiten des kindlichen Organismus. Ja. K. **28.** 1.
108. Lange: Ueber den Stoffwech. des Säuglings bei Ernährung mit Kuhmilch. Ja. K. **39.** 216.
109. Michel: L'Obstétrique. 1896. 15 Mars.
110. Keller: Phosphor und Stickstoff im Säuglingsorganismus. Ar. K. **29.** 1.
111. Rubner u. Heubner: Die natürl. Ernährung eines Säuglings. Z. B. **36.** 1.
112. Michel et Perret: Bull. Soc. d'obstét. de Paris. **1899.** 16 Mars.
113. Rubner u. Heubner: Die künstl. Ernährung eines normalen und eines atroph. Säuglings. Z. B. **38.** 315.
114. Berend u. Lange: Stoffwechselvers. an dyspept. Säuglingen. Ja. K. **44.** 339.
115. Bendix: Ein Stoffwechselvers. beim atroph. Säugling. Eng. A. Suppl. **1899.** 206.
116. Freund: Chlor und Stickstoff im Säuglingsorganismus. Ja. K. **48.** 137.
117. Freund: Wasser und Salze in ihren Beziehungen zu den Körpergewichtsschwankungen der Säuglinge. Ja. K. **59.** 421.
118. Keller: Zur Frage der Eiweissüberernähr. beim Säugling. C. i. M. **1898.** Nr. 21.
119. Keller: Ueber den Einfl. der Zufuhr von Kohlehydr. auf den Eiweisszerfall im Organismus magendarmkranker Säuglinge. C. i. M. **1899.** Nr. 2.
120. Keller: Malzsuppe, eine Nahrung für magendarmkranke Säuglinge. 1898.
121. Baginsky: Atrophie der Säuglinge. D. m. W. **1899.** Nr. 18.
122. Poppi: Il ricambio materiale nell' atrofia infant. con speciale riguardo al ricambio gassoso. Atti del IV. congr. pediat. ital. 1902. P. 106.
123. Heubner: Säuglingsatrophie. Ja. K. **53.** 35.
124. Demme: 12 Jahresb. des Jenner'schen Kinderspitals. **1875.** P. 18.
125. Biedert: Über das Verhalt. des Fettes im Kinderdarm und über Fettdiarrhœ. Ja. K. **14.** 336.

126. Szontagh: Über künstl. Säuglingsernährung. Ja. K. **56.** 341.
127. Heubner: Ueber die Ausnutz. des Mehles im Darme junger Säuglinge. B. k. W. **1895.** Nr. 10.
128. Carstens: Über die Ausnutz. des Mehles im Darme junger Säuglinge. V. G. K. **1895.** 169.
129. Heubner: Säuglingsdarm und Mehlverdauung. Ja. K. **47.** 134.
129a. Pautz u. Vogel: Ueber die Einwirk. der Magen- und Darmschleimhaut auf einige Biosen und auf Raffinose. Z. B. **32.** 303.
130. Orban: Ueber das Vorkommen der Laktase im Dünndarm und in den Säuglingsfäzes. P. W. **1899.** Nr. 33.
130a. Voit: Über das Verhalt. verschiedener Zuckerarten im menschl. Organismus nach subkutaner Injektion. D. Ar. M. **58.** 523.
131. Grosz: Über Glykosurie im Säuglingsalter, nebst Versuchen über alimentäre Glykosurie. Ja. K. **34.** 83.
131a. Langstein u. Steinitz: Laktase und Zuckerausscheid. bei magendarmkranken Säuglingen. Be. P. P. **7.** H. 12. 1906.
131b. Hofmeister: Ueber Resorp. und Assimil. der Nährstoffe. Ueber die Assimilationsgrenze der Zuckerarten. E. A. **25.** 240.
131c. Luzzatto: Über das Verhalt. von Laktose und Galaktose bei Hunden. E. A. **52.** 107.
132. Blauberg: Über den Mineralstoffwech. beim künstlich ernährten Säugling. Z. B. **40.** 1. 1900.
133. Blauberg: Ueber den Mineralstoffw. beim natürlich ernährten Säugling. Z. B. **40.** 36. 1900.
134. Söldner: Die Salze der Milch und ihre Beziehungen zu dem Verhalt. des Kaseins. Diss. Erlangen, 1898.
135. Voit: Über Sekretion und Resorption im Dünndarm. Z. B. **29.** 325. 1892.
136. Arndt: Das Verhalt. der Kalksalze in den Fäzes und im Harn von Säuglingen bei Darreichung gekochter und ungekochter Milch. Diss. Breslau, 1901.
137. Cronheim u. Müller: Über den Einfluss der Sterilisation der Milch auf den Stoffwechsel des Säuglings. Ja. K. **57.** 45.
138. Steinitz: Zur Kenntnis der chron. Ernährungsstörungen der Säuglinge. Ja. K. **57.** 689.
139. Keller: Gastroenteritis im Säuglingsalter. Ammoniak-ausscheidung. Ja. K. **44.** 25.
140. Keller: Chron. Ernährungsstörungen der Säuglinge. Fettumsatz und Azidose. Mo. K. **1.** 234.
140a. Freund: Zur Wirkung der Fettdarreichung auf den Säuglingsstoffw. Ja. K. **61.** 36.
141. Knöpfelmacher: Verdauungsrückstände bei der Ernährung mit Kuhmilch. 1898.
142. Müller: Ueber den organischen Phosphor der Frauenmilch- und Kuhmilchfäzes. Z. B. **39.** 451. 1900.
143. Knöpfelmacher: Über die Ausnutzung des Kuhmilchkaseins. Ja. K. **52.** 545.
143a. Schlossmann: Ueber Phosphors in der Milch. Ar. K. **40.** 1.
144. Camerer jun.: Die chem. Zusammensetz. des Neugeborenen. V. G. K. **18.** 201.
145. Scherer: Die Respiration des Neugeborenen und Säuglings. Ja. K. **43.** 471.
146. Camerer: Der Stoffwechsel des Kindes. 1896.
147. Cramer: Zur Stoffwechselgleichung beim Neugeborenen. Ar. K. **32.**
148. Johannessen u. Wang: Über die Ernährungsphysiol. des Säuglings. Z. p. C. **24.** 482.
149. Gaus: Ueber Nahrungsausnutz. bei Neugeborenen. Ja. K. **55.** 129.
150. Camerer: Beitr. zur Erforschung der stickstoffhaltigen Bestandteile des menschl. Urins, insbesondere der sogenannten Alloxurkörper. Z. B. **35.** 206. 1897.
151. Camerer: Zur Anal. des menschl. Urins. Z. B. **38.** 227. 1899.
152. Camerer jun.: Über die Ammoniakaussch. im menschl. Urin. Z. B. **43.** 13.
153. Pfaundler: Ueber Stoffwechselstör. bei magendarmkranken Säuglingen. Ja. K. **54.** 247.

154. KELLER: Welche Momente beeinflussen die Ammoniakaussch. im Harn magendarmkranker Säuglinge? Ja. K. **48.** 397.
156. CAMERER: Anal. vom menschl. Urin. Z. B. **45.** 1.
157. BRAUNSTEIN: Ueber die Harnstoffbestim. im Harn. Z. p. C. **31.** 381.
158. CAMERER: Die stickstoffhalt. Bestandteile im menschl. Urin und die sog. Azidose. Mo. K. **2.** 1.
159. VON OORDT: Das Verhältnis von Stickstoff und Kohlenstoff im Säuglingsharn. Z. B. **43.** 46.
160. KELLER: Phosphorstoffwech. im Säuglingsalter. Z. M. **36.** 1. 1898.
161. FREUND: Zur Kenntnis der chron. Ernährungsstörungen der Säuglinge. Mo. K. **1.** 230.
162. STEINITZ: Ueber den aliment. Einfluss des Fettes auf die renale Ammoniakaussch. C. i. M. **1904.** 81.
163. KELLER: Organische Phosphorverbind. im Säuglingsharn. Z. p. C. **29.** 146.
164. FREUND: Zur Kenntnis der Schwefelaussch. bei Säuglingen. Z. p. C. **29.** 24.
165. FREUND: Zur Kenntnis der Oxydationsvorgänge bei gesunden und kranken Säuglingen. V. G. K. **18.** 187.
166. ZAMFIRESCO: Albuminurie et Indicanurie chez le nouveau-né et le nourisson avec une étude sur l'urine normale. Thèse de Paris. **1898.**
167. HOCHSINGER: Ueber Indikanurie im Säuglingsalter. V. G. K. **8.** 28.
168. STEFFEN: Beitr. zu Indikanausscheid. bei Kindern. Ja. K. **34.** 18.
169. CONCETTI: Ricerche sulla indicanuria nelle malattie infantili. Ped. 6. **11.**
170. GEHLIG: Über Indikanaussch. bei Kindern, speziell bei kindlicher Tuberkulose. Ja. K. **38.** 285.
171. PORAK: R. m. M. C. **1878.** 334.
172. SKORMIN: Ueber die verschied. Formen des Ikterus im Säuglingsalter. Ja. K. **56.** 176.
173. PARROT ET ROBIN: R. m. M. C. **1879.** 374.
174. CRUSE: Beitr. zur Kenntnis des Icterus neonatorum. Ar. K. **1.** 353.
175. KNÖPFELMACHER: Das Verhalten des Gallenfarbst. im Harn beim Icterus neonatorum. Ja. K. **47.** 447.
176. EPSTEIN: Ueber die Gelbsucht bei neugeborenen Kindern. Vo. s. V. Nr. 180.
177. SCHRACK: Ueber Azetonurie u. Diazeturie bei Kindern. Ja. K. **29.** 411.
178. PARROT ET ROBIN: Sur l'urine des nouveau-nés. Ar. g. m. **187.** 6.
179. CRUSE: Ueber das Verhalt. des Harns bei Säuglingen. Ja. K. **11.** 393.
180. KOPLIK: Dietetic Glycosuria in Artificially-fed Infants. Ar. Ped. **9.** 781.
181. HECKER: Über hereditäre Syphilis. Habilitationssch. München, 1898.
182. NOBÉCOURT: De l'élimination par les urines de quelques sucres introduits par la voie digestive ou la voie sous-cutanée chez les enfants. R. M. E. **18.** 161. 1900.
183. TERRIEN: De la glycosurie aliment. chez les nourrissons. R. M. E. **18.** 402.
184. CZERNY U. A. KELLER: Handbuch (Lit. Nr. 2). P. 320.
185. CAMERER: Ueber das Nahrungsbedürfnis von Kindern verschiedenen Alters. V. G. K. **7.** 116.
186. SEDGWICK: Die Fettspaltung im Magen des Säuglings. Ja. K. **64.** 194.
187. CRONHEIM U. MÜLLER: Über den Stoff- und Kraftwechsel des Säuglings mit besonderer Berücksichtig. des organisch gebundenen Phosphors. Z. d. p. T. **6.** Nrs. 1 and 2.
188. HEUBNER: Die Energiebilanz des Säuglings. B. k. W. **1901.** Nr. 17.
189. HEUBNER: Die Energiebilanz des Säuglings. Z. d. p. T. **5.** Nr. 1. 1901.
190. REYHER: Beitr. zur Frage nach dem Nahrungs- und Energiebedürfnis des natürlich ernährten Säuglings. Ja. K. **61.** 553.
191. SCHLOSSMANN: Zur Frage der natürl. Säuglingsernährung. Ar. K. **30.** 288.—Weiteres zur Frage der nätürlichen Säuglingsernährung. Ar. K. **33.** 338.
191A. SCHKARIN: Beitr. zur Kenntnis des Säuglingsstoffw. bei Infektionskrankh. Ar. K. **41.** 81.
192. SJÖQVIST, cit. by HAMMARSTEN: Lehrb. d. phys. Ch. 4th ed. P. 421.
193. THIERNICH: Ü. Leberdegener. bei Gastroenteritis. Bc. A. P. 22. 176.

194. Van der Bergh: Gastroenteritis im Säuglingsalter. Ja. K. 45. 265.
195. Keller: Das Schicksal der Amidosäuren im Organismus des magendarmkranken Säuglings. C. a. P. 9. 739.
196. Kolsky: Ü. d. Einfl. der Ernährung a. d. Ammoniakaussch. im Harn bei Säuglingen. Diss. Breslau, 1897.
197. Czerny u. Keller: Zur Kenntniss der Gastroenteritis. Saurebildung. Ja. K. 45. 284.
198. Keller: Ü. d. Bedeut. der Azidität des Harns beim magendarmkranken Säugling. Ja. K. 47. 176.
199. Salge: Die Frauenmilch in der Therapie des acuten Dünndarmkatarrhs. Ja. K. 58. 641.
200. Langstein u. Meyer: Die Azidose des Säuglings. Ja. K. 63, 30. 1906.
201. Meyer: Zur Kenntniss der Phenolaussch. beim Säugling. Mo. K. 4. 344. 1905.
202. Langstein u. Steinitz: Die Kohlenstoff- u. Stickstoff-aussch. durch den Harn beim Säugling u. älteren Kinde. Ja. K. 61. 94.
203. Rubner u. Heubner: Beitr. z. Kennt. der Energiebilanz beim Säugling. Ja. K. 61. 429.
204. See Nr. 2. P. 77.
205. Terrien: De la gastro-entérite des nourrissons. R. M. E. 18. 1. 1900.
206. Lesné et Merklen: Étude des altérations et des fonctions du foie et du rein au cours des gastro-entérites des nourrissons. R. M. E. 19. 53. 1901.
207. Bell: Ar. Ped. 23. P. 194. 1906.
208. Kerley, Mason and Craig: Ibid. P. 489.
209. Salge and Hamburger: Ibid. P. 105.
210. Shaw and Gilday: B. M. J. 1906. Vol. ii., p. 932.
211. Tunnicliffe: Arch. Internat. de Pharmacodyn. et de Thérap. 1906.
212. Morse: Ar. Ped. 22. P. 561. 1905.
213. Rothschild: Révue d'Hygiene et Méd. Infant. 6. P. 603. 1905.
214. Hutchison: Goulstonian Lectures. L., 1904. Vol. i., p. 1261.
215. Wright: Army Medical Reports. 1895.
216. Cybulski: Calcium Metab. in Tetany. Mon. f. Kind. Bd. V. No. 8. 1906.
217. Würtz: Action of Bioferrin in Children. Med. Klinik. 1906. P. 1339.
218. Krasnogorski: Iron Interchange in Children. Russki Wratsch. 1906.

CHAPTER VIII

MINERAL WATERS AND METABOLISM

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Although many of the points in this chapter are dealt with in other parts of the work, the details are so scattered that it is worth while running the risk of repetition in order to deal comprehensively with the important subject of mineral-water treatment and its effect upon metabolism, for both the theory and practice of this subject have entered largely into every branch of medicine. But the very wealth of the literature makes it incumbent upon us to sift with the greatest care the facts from the fancies, since even the most modern work on the subject in many instances scarcely rises above the level of purely superficial compilation.

Valuable scientific work has, however, been published during the last ten years in spite of the enormous output of worthless pseudo-scientific writings which mislead the inexpert. A clamorous jargon has been invented, which includes apparently learned expressions about delayed or increased metabolism, oxidation, assimilation, protein balance, molecular disintegration, ions, osmosis, radio-activity, and the like; without these no twentieth-century advertisement is complete. The truth is that so little is known of the bearing of mineral waters on biological processes that most of the statements in balneological literature may be stigmatized as idle make-believe. When we pick out from the trash the material of real value which can help to settle the many points under discussion, very little remains at our disposal, and of this a certain proportion will be found treated of in other chapters, especially the volume on physiology and the section on pharmacology [*cf.* also Glax (1)].

Without entirely neglecting the other aspects, this chapter will be devoted mainly to the general therapeutic effects of mineral waters, for it has not been determined how far the combined action of their individual constituents as ascertained by chemical analysis coincides with the action of the natural waters themselves (2).

The hopes raised by the new physical-chemical methods first applied to mineral waters by Köppe (3) have not been realized, and the many contradictions between theory and practice are still unexplained; yet the value of the modern work must not be cried down because its practical application is not immediately apparent (4). Far less must the

new aspects be rashly exploited as some novel gospel of balneology. A superficial and discreditable literature has sprung up, which trades upon the catch-word " metabolism," just as a previous generation of charlatans misapplied the magnificent achievements of Bischoff, von Voit, and von Liebig. In the meantime it must be allowed that many empirical facts which as yet cannot be made to harmonize with the requirements of exact science merit some attention as proven facts (5), but there is no justification for perverting both facts and science into fearful and wonderful hypotheses.

I.—BALANCE OF ENERGY.

When the numerous statements that certain mineral waters can affect the metabolism in one direction or another are traced to their fundamental facts, it is found that they are based upon a slight increase in the output of urea as the result of free water-drinking under certain conditions. From this is argued an increase in the processes of oxidation, while colour is lent to the idea from the undoubted action of alkalis in promoting the oxidation processes in the chemical laboratory.

In this way might the value of " water-cures " in obesity, gout, and diabetes be explained; for the stimulation of the oxidizing processes should increase the fat balance, the formation of urea from uric acid, and the process of glycolysis and oxidation of sugar.

A.—PLAIN WATER.

Water-drinking undoubtedly affects the consumption of energy, but only to a slight extent, and quite temporarily; very large quantities of water must be taken to produce even this slight effect. At present the potential energy exerted by the intestines in absorption, the heart in circulation, or the glands in excretion of the additional bulk of water cannot be estimated. Bidder and Schmidt (6) found in a cat that the inorganic balance (measured by CO_2) was not increased by drinking very large quantities of water. Loewy (7) confesses that the slight increase in the oxygen consumption he found in the human subject after small amounts of cold water (100 c.c.) were quite within the limits of experimental error.

Speck (8) made an interesting observation: If a large quantity of water is drunk at intervals during the night before the experiment (which was carried out before breakfast), it does not affect the oxygen consumption, CO_2 output, or heat production; but if the same amount (1,250 c.c.) is taken at once just before the experiment, each of these is considerably increased. The difference amounted to about 8 per cent. (oxygen increased from the normal 301 to 325). These results are confirmed by some unpublished researches carried out by Schmidt under von Noorden's direction. After drinking 1 litre of water (at 12° C.) the oxygen consumption rose in a quarter of an hour to 41·2 c.c. (20 per cent.), falling, however,

to normal after three-quarters of an hour. The total increase amounted to 1,200 to 1,800 c.c. oxygen, representing 5·8 to 8·6 calories, but this is much too little to be reckoned as a factor in increasing metabolism.

Such a state of affairs only occurs after drinking much greater quantities of water than come within the range of practical treatment. Von Noorden (6) gives the following example : A boy, aged ten years, suffering from diabetes insipidus, for whom 1,500 calories was ample nourishment, drank daily about 8 litres of water besides that contained in his "solid" food ; the warming of this from 12° C. to body-heat requires alone 200 calories, equivalent to an increased exchange of about 13 per cent., without considering at all the increased demands imposed by the additional work of the intestines and glands.

B.—SALT SOLUTIONS AND MINERAL WATERS.

Only aperient waters have been investigated ; their effect on the stomach and intestines is greater than that of plain water (glandular activity and peristalsis), and while their effect lasts, the rate of metabolism is increased. A table of Loewy's is appended, giving the results of administering 7·5 to 15·0 grammes of Glauber salts in 200 c.c. of water :

Increased Oxygen Consumption per Minute.

Period.	*Minimum.*	*Maximum.*	*Average.*
Minutes.	c.c.	c.c.	c.c.
15	− 4·7	+58·6	+18·1
30	+34·7	+34·7	+34·7
45	+ 0·7	+84·3	+16·1
60	− 1·7	+29·7	+ 8·4
75	−27·2	+81·7	+ 7·1
90	+ 3·0	+58·8	+20·3
105	−20·0	− 6·2	−13·1

The individual results vary so much, and the number of observations is so small, that it would be misleading to take these averages as conclusive ; they make it appear that in the first ninety minutes an average of 1,270 c.c. of oxygen was consumed in excess of the amount without the administration of Glauber salts, an increase of 6·0 calories. According to this reckoning, 1 litre of oxygen corresponds to 4,831 calories or 0·5 gramme of fat.

Salomon determined the minimal metabolism, and then administered 750 c.c. Kissingen Rakoczy water at a temperature of 12° C. This quantity was drunk in four minutes, and there resulted the following increased consumption of oxygen :

First experiment, within 195 minutes, 4,932 c.c. =25·3 c.c. per minute.
Second „ „ 150 „ 3,210 „ =21·4 „ „

In the first case the total number of calories liberated by the mineral water taken was 23·8, and in the second 15·5 (= 2·5 and 1·7 grammes of fat respectively).

Both Loewy and Salomon found a short period of diminished oxygen intake immediately after the period of excitation in many cases.

There does not seem to be so definite a law governing the amount of increase in the case of water as there is for solid food : temporary and individual variations in the susceptibility of the alimentary canal may account for the differences. The recent investigations in Frankfürt tend to prove the correctness of clinical experience that the mineral waters which stimulate the intestines do actually " increase metabolism." Theoretically it seems conceivable that this increase not only concerns the " resting value " (minimal exchange), but that as soon as the oxidation processes are stimulated in any direction—*e.g.*, the intestines—all the others share in the excitation (a " dynamic influence," as Rubner describes it) ; but this needs further proof, and it must be remembered that nothing is yet known concerning the individual effects of the bulk of water, its temperature, constituent salts, molecular concentration, and CO_2 contents.

Many other factors, muscular action, baths, etc., contribute to the treatment at health resorts, and all of these tend to raise the exchange of energy, while the water-drinking takes an important share in the general effect, especially by its action on the stomach and intestines, which aids in the carrying out of the diet prescribed.

Loewy (10) has recently found in a castrated dog that the gaseous exchange was increased 30 per cent. when 3 grammes of soda (0·23 gramme per kilogramme) were administered daily ; but in a second experiment he found no such increase. However, such quantities as this are never given in any " water-cures."

Previous mention has been made of the alkalis. The test-tube experiments upon their catalytic influence in fermentation do not concern us here [Schade (11)], less still their power of preventing the oxidation of uric acid and the breaking down of sugar.

Since facts and not hypotheses are our only interest at present, we must be content with recognising the possibility that the continued administration of a particular mineral water may alter the inorganic composition of the tissues, and that, consequently, the breaking down or building up of some individual " atom-complex " (sugar or uric acid) may be—catalytically, perhaps—hastened or retarded.

LITERATURE.

1. Glax : Lehrb. der Balneotherapie. 1897-1900.

2. Leichtenstern : Balneotherapie, in von Ziemssen's Handb. d. allg. Ther. 1880.—Liebreich : Bemerk. über künstl. Mineralwässer und Salzmischungen. Verhdl. der Balneol. Ges. 9 März, 1895 ; The Therap. Value of Alkaline Waters of the Vichy Type. B. M. J. 1902. 11 October.

3. Köppe : Physikal. Chemie in der Medizin. 1900. Die physikal. chem. Analyse der Mineralwässer. Arch. Balneother. 1. H. 8. 1898.

4. Paul : Die Bedeut. der Jonentheorie für die phys. Chemie. 73. Naturf-Vers. 1. 139. 1902.—His : Die Bedeut. der Jonentheorie in der klin. Medizin. Ibid. 165.—Meyerhoffer : Die chem.-physikal. Beschaffenheit der Mineralquellen.

1902.—Roloff: Genügt die chem. Analyse für die therap. Beurteilung der Mineralwässer? 1903.—Roloff: Physikal.-chem. Grundlage für die therap. Beurteil. der Mineralwässer. T. M. **1904.** 445.—Hamburger: Osmotischer Druck und Jonenlehre in den medizin. Wissenschaften. 1904.

5. von Noorden: Ueber den Einfl. der schwachen Kochsalzquellen auf den Stoffw. des Menschen. 1896.

6. Bidder u. Schmidt: Die Verdauungssäfte und der Stoffwechsel. P. 345. 1852.

7. Loewy: Ueber den Einfl. der salin. Abführmittel auf den Gaswechsel des Menschen. Ar. P. M. **43.** 515. 1888.

8. Speck: Phys. des menschl. Atmens. P. 42. 1892.

9. von Noorden: Pathol. des Stoffwechsels. P. 141. 1893.

10. Loewy: Bemerk. zur Wirkung der Borpräparate auf den Stoffwechsel. Eng. A. **1903.** 378.

11. Schade: Ueber katalytische Beeinflussung der Zuckerverbrennung. Mü. m. W. **1905.** 1088 and 1713.

II.—PROTEIN METABOLISM.

An explanation has been given in the volume on Physiology (Vol. I., p. 402) of a phenomenon which frequently occurs when larger quantities of water are taken than usual, and von Noorden has shown that the increased nitrogenous excretion seen during the first few days is not really an indication of increased protein disintegration, but may be compared to a complete clearing out of all residual waste products which, under other circumstances, are not necessarily excreted immediately they are formed. This can be observed in certain diseases where too little water is drunk [Mohr (1)]. Among the pseudo-scientific virtues which are attributed to every marketable mineral water the fact is always paraded—which no one denies (2)—that the water promotes the output of waste albumin products, and to this is added, "and therefore increases the rate of protein metabolism," a process which is neither proved to exist nor, when present, to be beneficial. Still, it sounded well, and made a good catch-phrase, until von Noorden and Dapper (3) demonstrated that occasionally as the result of "water-cures" the output of proteins really did exceed the intake with unpleasant and damaging effects on the subject of the cure, in whose individual case the water practically behaved as a poison; dismay seized upon the "prospectus writers," and the best advertisements now read, "These waters are guaranteed to have no effect on the protein metabolism"! There are very few researches of any value on this point. The earlier work on Friedrichshall water was contradictory (4), von Mering alone finding the daily output of urea a little above the normal. Of course, the methods were not at all in accordance with the standard required to-day for similar investigations, an objection which may be urged against London's (5) otherwise most exact research with Carlsbad water; for the food was only weighed, not analyzed, so that, as the author admits himself, the considerable decrease of nitrogenous output cannot be accepted as absolutely proved. Improved methods make Leva's (6) work on Tarasper water of more importance.

Table of Nitrogen Output in Urine and Fæces. Food Nitrogen estimated at 18·69 Grammes.

	Grammes.
Without Tarasper water	18·78
With 400 grammes Lucius spring water	18·81
„ 400 grammes plain water	19·60
„ 800 to 1,000 grammes Lucius water	21·40
„ 800 to 1,000 grammes plain water	20·60

Leva considered that increased amounts of Lucius water (period 4 and after-period 5) caused an increase in the protein balance; he even suggests a "loss of muscle substance." Seeing how few experiments upon nitrogen output exist, greater importance attaches to an accurate measurement of nitrogen intake, but Leva only made a single analysis of the total food nitrogen before the food had been cooked. Since milk and uncooked food together made up 10 grammes nitrogen, or half the intake, their variations alone might account for more than the whole variation in the protein balance. Leva himself points out the objection as a warning of the way in which a painstaking research may be robbed of its value by a very slight flaw in the method. Later experiments with other waters make it difficult to suppose that Tarasper water really possesses unique properties of disturbing the protein balance. The general tendency to an increased nitrogen output depends on the small "calorie intake."

Genth's (7) experiments on Langenschwalbach Weinbrunnen water (carbonate of iron) are interesting, although incomplete (no analysis of food and fæces).

	Urea.	*Period.*
Constant diet without water	39·8 grammes	6 days.
„ „ with 1,000 grammes plain water ..	41·9 „	7 „
„ „ with 1,000 grammes iron water ..	42·5 „	14 „
„ „ without water (after period) ..	39·7 „	3 „

Genth arrives at the conclusion that with this water an increase of oxidation and disintegration of the proteins take place, so that great caution should be exercised in prescribing it for anæmic girls. So sweeping an assertion requires a surer foundation than the faulty methods on which this is based.

The first series of investigations where errors in method were excluded was undertaken by von Noorden (3) and Dapper (8) on the subject of metabolism and obesity in 1893. The Kissingen Rakoczy and bitter waters were used, and the question of storing up of proteins was carefully considered from every standpoint. In the short communication made at the Berlin Medical Congress von Noorden said: "In spite of all that has been written about the increase of urea excretion with these waters, there is absolutely no evidence of increased protein disintegration." Since the experiences of various authorities were so contradictory, Katz (9) undertook to examine the same problem with the stronger saline water of the Harzburg Crodo Spring, and in order to make the external conditions as unlike as possible, he did not work in von Noorden's laboratory, but in the Zuntz Institute. These and all the later experiments per-

formed with reliable methods gave the same negative result, although in many instances the subjects would not be considered very favourable so far as stability of protein balance is concerned (cases of obesity and severe diabetes). The conditions were uniform throughout these exhaustive investigations. Examples of the available figures on this subject are recorded in the following table :

Disease.	*Period.*	*Food Nitrogen.*	*Intake in Calories.*	*Nitrogen Balance (Average per Diem).*	*Remarks.*
	Days.	Gm.		Gm.	
Obesity [Dapper (10)] ..	9	14·86	1,491	+0·14	No mineral water.
	9	14·72	1,292	+0·46	400 to 900 c.c. Rakoczy daily.
	14	14·90	1,157	+0·61	300 to 900 c.c. Rakoczy and 200 c.c. Kissingen bitter water.
Healthy subject [Katz] ..	4 (fore period)	17·14	2,918	+1·58	No mineral water.
	5	17·14	2,918	+1·36	1 day. 420 c.c. Crodo water. 4 days. 1,050 c.c. Crodo water.
	3	17·14	2,918	+1·59	No mineral water.
Chlorosis [Henius (11)]	7 (fore period)	11·5	1,811	+0·35	No mineral water.
	22	11·7	1,811	+0·35	300 to 800 c.c. Val Sinistra water daily.
Obesity [Ludwig (12)] ..	4	15·65	2,487	−0·58	No mineral water.
	8	18·16	2,487	+0·19	1,500 c.c. Carlsbad Mühlbrunnen daily.

Further experiments with Carlsbad, Apenta, Mergentheim, and Levico waters gave similar results (13). In a few other instances a very small nitrogen loss was observed. This was partly within the limits of experimental error and partly due to the washing out of residual waste. It may be accepted as certain that mineral waters containing sodium chloride and neutral salts do not increase the rate of albumin metabolism. As regards arsenical waters, one thing only is known—namely, that protein assimilation is favourably affected (11, 13, 14); there are no exact figures dealing with iron-containing waters.

LITERATURE.

1. Mohr: Ueber das Ausscheidungsvermögen der kranken Niere. Z. M. **51.** 331. 1903.

2. Oppenheim: Phys. und Path. der Harnstoffaussch. Ar. P. M. **23.** 446. 1881.—Mayer: Ueber den Einfl. der vermehrten Wasserzufuhr auf den Stoffumsatz. Z. M. **2.** 34. 1880.

3. von Noorden u. Dapper: Ueber den Stoffw. fettleibiger Menschen bei Entfettungskuren. B. k. W. **1894.** Nr. 24.—Dapper: Ueber den Einfl. der Kochsalzquellen auf den Stoffw. des Menschen. Z. M. **30.** 371. 1896.

4. Mosler: Ueber die Wirk. des Friedrichshaller Bitterwassers. Diss. Marburg, 1860.—von Mering: Ueber den Einfl. des Friedrichshaller Bitterwassers auf den Stoffwechsel. B. k. W. **1880.** 153.—Markwald: Ueber die Wirk. des Friedrichshaller Bitterwassers. D. m. W. **1886.** 391.

5. London: Ueber den Einfl. des kochsalz- und glaubersalzhalt. Mineralwassers auf einige Faktoren des Stoffwechsels. Z. M. **13.** 1888.

6. Leva: Ueber die Einwirk. des Tarasper Wassers auf den Stoffwechsel. B. k. W. **1394.** Nr. 11.

7. Genth: Ueber die Veränderungen der Harnstoffaussch. bei dem innerl. Gebrauch des Schwalbacher Eisenwassers. D. m. W. **1883.** 403.

8. Dapper: Stoffw. bei Entfettungskuren. Z. M. **23.** 113. 1893.

9. Katz: Einfl. der Harzburger Crodoquelle auf den Stoffwechsel. Diss. Berlin, 1894.

10. Dapper: Ueber Entfettungskuren. Ar. V. **3.** 1. 1898.

11. Henius: Ueber das arsenhaltige Wasser von Val-Sinestra und seine Wirk. auf den Stoffwechsel. D. m. W. **1904.** 949.

12. Ludwig: Ueber den Einfl. des Karlsbader Wassers auf den Stoffwechsel. C. i. M. **1896.** Nr. 46.

13. Brandenburg: Beitr. zur Wirk. von Bestandteilen des Karlsbader Wassers. T. M. **1899.** 633.—Jacoby: Ueber den Einfl. des Apentawassers auf den Stoffw. einer Fettsüchtigen. B. k. W. **1897.** 248.—Allard: Ueber den Einfl. eines natürl. Bitterwassers auf den Stoffw. bei Diab. mell. und bei Fettsucht. Z. M. **45.** 340. 1902.—Schreiber: Einfl. des Levikowassers auf den Stoffwechsel. Mü. m. W. **1902.** 1490.

14. Ewald u. Dronke: Über den Verlauf des Stoffwech. bei längerem Gebrauch des Leviko-Arsen-Eisenwassers. B. k. W. **1892.** Nrs. 19, 20.

III.—INFLUENCE OF MINERAL WATERS ON THE STOMACH.

A.—CHANGES IN MOLECULAR CONCENTRATION.

Winter and Köppe (1) have made a special study of the molecular concentration of secretions generally. In their researches on the gastric juice they found the molecular concentration in the starving state was, on an average, $-0{\cdot}45°$ (lowering of freezing-point, or Δ). Strauss (2) has, however, placed the normal at $-0{\cdot}38°$, and Pfeiffer and Sommer (3) in exceptional cases found it as low as $-0{\cdot}55°$. It appears, therefore, that $-0{\cdot}45°$ may be regarded as a fair average.

The following table gives some of Strauss's results:

Disease.	*Cases.*	*Molecular Concentration.*
Hypersecretion	—	$\Delta = -0{\cdot}35°$ to $-0{\cdot}39°$
Atony with hypochlorhydria	13	$\Delta = -0{\cdot}45°$ or over
	12	$\Delta = -0{\cdot}45°$ to $-0{\cdot}50°$
	2	$\Delta = -0{\cdot}50°$ to $-0{\cdot}55°$

Strauss and Roth (4) advance the view that after food the organism strives to establish a molecular concentration of its contents, in which $\Delta = -0{\cdot}45°$ by a process of ebb and flow. This figure they regard as the physiological optimum which, when reached, is maintained (the so-called "gastro-isotonic" concentration). They suggest that directly this point is departed from the secretion of hydrochloric acid and ferments begins.

In the stomach the optimum of molecular concentration ($-0{\cdot}45°$) is materially different from that of the blood-serum ($-0{\cdot}56°$).[1]

The presence of hydrochloric acid in the stomach probably accounts for some part of the variation ; in the blood-serum the chlorides may add about $-0{\cdot}36°$ to Δ, a figure which approaches that of the gastric juice.

The variations in the molecular concentration in the stomach due to the ingestion of food can be well studied with saline solution or mineral waters. According to Strauss and Roth, there are three processes working in combination :

1. Diffusion takes place between the blood and the stomach contents, in order to equalize the differences in the total and partial osmotic pressures of the ingesta and components, bringing them to the level of the blood.

This process is guarded by the fact that the water does not pass from the stomach to the blood [von Mering and Moritz (5)], although, according to Bönniger (6), a slight absorption of water may take place.

2. A diluting secretion (*Verdünnungssekretion*) exudes from the mucous membrane, and tends to lower the osmotic pressure, even in opposition to the mere physical forces at work. This involves some expenditure of energy comparable to that required in the kidney to produce a secretion having a higher osmotic pressure than the blood-serum.

3. A specific digestive secretion, produced by the glandular epithelium (HCl and ferments), whose effect is to raise the osmotic pressure, and in some degree to counteract the " diluting secretion."

Strauss and Roth further found that—

(*a*) On the introduction into the stomach of fluids having a higher osmotic pressure than the blood (hypertonic), processes 1 and 2 take place until the stomach contents have reached the optimum (gastro-isotonic concentration). No. 3 is for the time being delayed. The general effect is that the stomach retains its contents for a longer time during this process of adjustment than is required when the molecular concentration of the ingesta is lower to begin with.

(*b*) With blood-isotonic solutions the process of diffusion goes on between the individual constituents, but is outbalanced by the diluting secretion, so that, in spite of contrary physical impulses, a hypotonic solution is actually produced. The specific secretion (No. 3) appears earlier than in the former case.

(*c*) The results with blood-hypotonic solutions are not uniform. Sometimes the diluting secretion seems to gain the upper hand, and cause a still further reduction of osmotic pressure ; occasionally the specific secretion preponderates, and raises the total concentration almost to isotony. The amount of specific secretion is greater with hypo- than with hypertonic solutions.

Having studied the behaviour of simple solutions, that of the mineral waters were next investigated. Strauss (7) states that the stay of a

[1] In dogs a similar difference exists [Sasaki, 3*b*] :

Blood Δ	$= -0{\cdot}60°$ to $-0{\cdot}62°$
Δ of gastric juice after " sham-feeding " with beef	$= -0{\cdot}46°$ to $-0{\cdot}57°$
Average	$-0{\cdot}53°$

mineral water in the stomach is more protracted, and the appearance of HCl retarded, when the molecular concentration of the water is high. Von Kostkewicz (8) has shown that almost every mineral water used medicinally or at table is either isotonic or hypotonic ; in table waters where we are free to choose, preference is instinctively given to a water of low molecular concentration if the osmotic pressure of the food is high, or else, to arrive at the same conditions, the richer our food the more salt we eat—a natural and empiric practice based upon the physiological needs of the organism. It is now possible to appreciate how it is that some very sensitive patients complain that certain waters, such as Salzschlirf Bonifacius, Tarasp Lucius, and Homburg Elizabeth Spring, which have a relatively high molecular concentration, " lie heavy on the stomach "; from clinical experience the Elizabeth Spring is known to be unsuitable in cases of chlorosis with hyperæsthesia of the stomach.

Waters of this class require a longer diluting period in the stomach, so that the length of stay in the stomach becomes a question of quality, not quantity. According to Pfeiffer and Sommer, waters containing sulphate of magnesia and bitter waters generally remain much longer in the stomach than do solutions of sodium chloride having the same osmotic pressure.

Kostkewicz gives the following table of some of the principal waters, arranged according to their molecular concentration :

Name.	Δ.
Kissingen bitter water	−1·110°
Friedrichshall bitter water	−1·080°
Apenta water	−1·015°
Salzschlirf Bonifacius	−0·892°
Tarasp Lucius Spring	−0·680°
Homburg Elizabeth Spring	−0·627°
Wiesbaden Kochbrunnen	−0·483°
Kissingen Rakoczy	−0·470°
Marienbad Kreuzbrunnen	−0·435°
Vichy Grande Grille	−0·330°
Carlsbad Sprudel	−0·275°
Wildungen Helene Spring	−0·230°
Homburg Louisa Spring	−0·217°
Ems Kränchen	−0·170°
Fachingen	−0·155°
Levico	−0·112°
Neuenahr Sprudel	−0·087°
Roncegno	−0·030°
Schwalbach chalybeate	−0·025°

A brief outline of Strauss's experiments will illustrate the changes in molecular concentration which occur in the stomach :

Water.	*Amount Taken.*	Δ *of Mineral Water.*	Δ *of Residue after 40 Minutes.*	*Amount of Residue after 40 Minutes.*
	c.c.			c.c.
Apenta	400	−1·02°	−0·75°	266
Püllnaer bitter water	400	−0·59°	−0·46°	110
Karlsbad Felsen	400	−0·25°	−0·32°	30

Pfeiffer and Sommer, working simultaneously with Strauss, found that isotonic solutions tend to remain isotonic, and that hypotonic solutions do not become still further diluted, but rather tend to increase in molecular concentration. In some individuals great disparity of results were obtained, even though the general tendency was in accordance with this rule. The conclusion may be accepted that the higher the molecular concentration of a fluid, the longer will be its stay in the stomach. In a later research, Pfeiffer (10) demonstrates that a dilution of isotonic fluids occurs, and concludes that as the result of the combined effects of physical forces and cellular activity the stomach strives to impart to its contents a molecular concentration of about $-0{\cdot}45°$. Strauss considers that very dilute solutions—*i.e.*, with freezing-point about $-0{\cdot}35°$—become still further diluted. Bönniger (6) does not confirm this, however. In his experiments with rabbits, he took the precaution of ligaturing the cardiac and pyloric orifices, so as to exclude all extraneous influences from the digestive processes. By this method the striking undulations of fluids and salts which Strauss described were entirely absent. The stomach practically does not change the molecular concentration of its contents in any way, or at most very slightly, in the direction of the osmotic pressure of the blood. There was no trace of Strauss's " diluting secretion."

Similar observations made in a man with non-malignant pyloric stenosis gave the like negative results.

Bönniger absolutely contradicts Strauss, and maintains that the " diluting secretion " does not exist, but that the dilution observed was only due to the saliva swallowed. This fact he further demonstrated upon himself. Saline or grape-sugar solutions whose Δ was $-0{\cdot}53°$ to $-0{\cdot}545°$ yielded $-0{\cdot}46°$ or $-0{\cdot}50°$ after a certain length of time in the stomach. If, however, a stomach-tube was retained in the œsophagus during the course of the experiment, so as to prevent the swallowing of saliva, the figures at the end were $-0{\cdot}50°$ to $-0{\cdot}56°$.

Some important investigations have been made upon patients with complete stricture of the œsophagus and gastric fistula (12). Here it was found that hypertonic solutions, indeed, approach isotony, but from absorption of sodium chloride rather than from any " diluting secretion." When this process is finished, such solutions (in spite of Strauss) remain hypertonic. Otto (12A) corroborates this by experiments on animals, showing a concentration rather than dilution of hypotonic solutions, and agreeing with Bönniger that the " diluting secretion " is really only saliva which Strauss overlooked. Even the connection between the osmotic pressure and the secretion of HCl could not be confirmed.

This point, whether hypotonic ingesta become still further diluted in the stomach, has attracted a good deal of attention, and called forth very discordant opinions (6, 12, 12A, 13, 13A).

It is agreed that the secretion and swallowing of saliva does not affect hypertonic ingesta in the slightest [Kress (13)].

Bickel's experiments upon dogs (13A) show that the dilution of hypotonic solutions is not by any means invariably the rule. Having,

by Pawlow's operation, made a so-called " small stomach," he introduced some Wiesbaden Kochbrunnen water, which is markedly hypotonic to the dog's blood and gastric juice. In every case the stomach contents became more concentrated within half an hour, occasionally becoming actually hypertonic.

Number of Experiment.	*Δ of Contents at Beginning.*	*Δ of Contents after Thirty Minutes.*
1	-0·37°	-0·40°
2	-0·39°	-0·52°
3	-0·39°	-0·68°
4	-0·43°	-0·45°
5	-0·40°	-0·75°
6	-0·37°	-0·53°

The non-electrolytes play an important but varying part in raising the molecular concentration, but such marked changes in concentration must be due to some active gland secretion, and not merely to the physical processes of osmosis.

In spite of his untenable theory of the " diluting secretion," Strauss has shown clearly that from a clinical standpoint the fact that the higher the molecular concentration of a mineral water the longer it remains in the stomach cannot be neglected. Hypertonic mineral waters must be avoided in gastric hyperæsthesia, in atony, and other forms of deficient motility. Whenever such waters are taken, a sufficiently long time must elapse before eating, so that the difference in osmotic pressure between the mineral water and the blood may be adjusted before the food enters the stomach. Practically, this point has long been observed, for it is a rule at all spas that waters of high molecular concentration are only to be taken in the early morning—as long as possible before breakfast—the table waters taken at or between meals being those of lower molecular concentration.

B.—EFFECTS OF MINERAL WATERS ON THE COMPLETION OF GASTRIC DIGESTION.

All the earlier investigations simply dealt with the chemical and mechanical aspects of digestion, observations being made on the effects of mixing the particular constituents of the water—sodium chloride, Glauber salts, soda, etc.—with the food, and estimating the amount of HCl secreted, and the rate at which the stomach discharged its contents into the intestine.

These experiments possess a pharmacological interest, but for investigating the " water cure " the method is not only valueless, but misleading. Its application explains many contradictions between theory and practice, and is responsible for the rise of many prejudices.

The improvement seen in various disorders of the stomach after

drinking certain quantities of a particular water at some famous spa has very likely nothing to do with either the water or its components. The condition of the gastric mucosa is probably quite as favourably influenced by exercise and limited feeding—two factors which in other diseases require time to produce their effects, but of which a single application is a ridiculous notion.

Hence, to compare short periods, and to claim for such researches scientific accuracy, or to make important deductions therefrom, is quite unreasonable.

From such investigations, however, material facts are sometimes gathered which clear the ground for a comprehensive and detailed study of the problem. It is only in disease that any experimental results need be expected.

It is a droll conceit that a healthy stomach which adapts itself uncomplainingly to the many and varied freights it has to carry in ordinary life can be completely thrown out of gear by so simple a means as one or two tumblers of mineral water daily.

From our ignorance of the pathogeny of digestive disorders, and from our still greater ignorance of the *point d'appui* of mineral waters in their cure, we must not be surprised if on occasions seemingly opposite conditions (sub- and hyperacidity) are improved by the same means. To argue, as is done, that because simple saline waters are beneficial in subacidity, therefore they are contra-indicated in hyperacidity, is a form of cleverness which rejects facts and opposes the free growth of knowledge.

Between honest ignorance of the mode of action of the " water cures " and the impudent assertions of charlatans there has arisen a scepticism which depreciates the value of the " mineral water," and suggests other factors, especially diet, as responsible for the general result. Diet has certainly a great deal to do with the cure, but to detract therefore from the value of the water-drinking does not seem to square with the facts.

On the one hand, strict diet without the other conditions of the " cure " is not entirely a satisfactory form of treatment ; and, on the other hand, the " waters " alone sometimes effect a cure in spite of the most unsuitable diet, all of which only goes to prove the limits of our knowledge of the digestion and of mineral waters. Boastful theories do not help to diminish our ignorance. Recently, however, practical efforts have been made which have yielded instructive results.

1. Mineral Waters taken simultaneously with Food.

(*a*) *Aerated Table Waters.*

The chief constituent in all so-called table waters which in any way affect digestion is CO_2. Waters which contain much CO_2 stimulate the appetite. According to the proverb, " Hunger is the best sauce," we might expect them to increase the gastric secretion. Following upon the preliminary and inconclusive experiments of Quincke (in dogs), Lockhart Gillespie (14) and others (in men), some definite results have

been obtained. Penzoldt (14) states that ½ litre of cold aerated water taken with a meal accelerates and increases the secretion of HCl, and terminates digestion in the stomach by the discharge of chyme into the small intestine sooner than the same amount of plain water. Liebreich (15) corroborates this, and Becker's (16) skilful experiments under Pawlow's guidance show that aerated waters taken into the stomach stimulate pancreatic secretion, while alkalis diminish it. The other waters which can, when taken with food, promote the digestive processes are weak salines (0·3 per cent. NaCl), or weak alkaline waters, such as Fachingen, Salzbrunnen, Kronenquelle, Vichy, Celestin, etc.

(*b*) *Saline Waters.*

The disputed question of the effect of sodium chloride on digestion in the stomach may be disregarded for the moment. It is admitted that such small amounts as we are now discussing make no difference. Very large doses such as are never given medicinally may lessen the secretion of HCl, interfere with peptonization, and delay the emptying of the stomach. The total salt taken in table waters is, however, as nothing in comparison with the amount consumed as a condiment.

The experiments of Bergell and Bickel (18) contain an idea, pregnant with meaning perhaps for the future, but at present inconclusive, that the retarding effect on the peptonizing process which certain saline waters exert—*e.g.*, Wiesbaden Kochbrunnen—is only found when the water has lost its radio-activity. The presence of the radium emanation, although by itself inactive as regards the process of secretion, either abolishes the retarding power of saline water or overcompensates it. Incomplete as they are, these researches are of great moment, because for the first time they enable us to grasp some notion of the real difference between the physiological workings of a water taken fresh from the spring full of radio-activity and those of the same water stale and altered by transport and storage.

(*c*) *Alkaline Waters.*

Allied to the effect of a weak saline water, it seems from the foregoing, may be that of alkaline waters, which, although the alkaline content is very small, form an unusual addition to the meal.

Disregarding fresh milk and eggs, all ordinary food has a neutral or faintly acid reaction, and under any circumstances the stomach may be supposed to render the whole of the ingesta strongly acid in a very short time. Evidently then, alkalis can only be indicated if their effect is to stimulate a free secretion of acid after a previous phase of subacidity, or when we wish to counteract hyperacidity.

Very little is known about the subject, yet the use of alkaline table waters increases in popularity every year, although it is not impossible that the practice may of itself cause grave disorders of the stomach. (Vichy Celestin contains 5·1, Biliner 4·6, Fachinger 3·6 grammes $NaHCO_3$ per litre.) Leube (19) and others (20) began the work, and Abend (20) has recently shown that ·05 to 1·0 gramme $NaHCO_3$, taken with a

test breakfast, has the immediate effect of neutralizing the HCl. This deficiency is however soon made good, and in the second half of the period of digestion the amount absolutely coincides with that found when the sodium carbonate is not given.

Du Mesnil (20) found that 1 to 2 grammes $NaHCO_3$ or 100 to 200 c.c. of Carlsbad Mühlbrunnen water (more than is ever given in practice) slightly increased the HCl, while 5 grammes caused a lasting diminution throughout the whole period of digestion. But even these results are within the limits of normal variation, and therefore prove nothing, as Ewald (20A) long ago hinted.

Linossier and Lemoine's observations on a man who ruminated are just as inconclusive where 1·0 gramme $NaHCO_3$ taken with the test breakfast, or 5 grammes an hour before, seemed to stimulate the secretion of HCl to its utmost. Reichmann (21) arrived at the opposite conclusion, but he gave his soda solution (amount not stated) half an hour after the test breakfast. Pawlow (22), from his experiments in animals, remains very sceptical about this stimulating effect of the alkaline carbonates; at any rate, it probably does not amount to more than the actual acid required for their neutralization, after which the usual amount of HCl, whether normal or deficient, is secreted.

The most trustworthy results are those of Schüle (23), who, however, worked with much larger amounts than are ever used in practice (7 grammes with a test meal consisting of 400 c.c. of cornflour gruel). In certain subjects whose normal acidity was rather low the alkali markedly decreased the total during the whole period of digestion, so that often no free HCl could be detected; in other cases the deficiency soon gave place to an increased secretion, so that after fifteen or twenty minutes the amount rose to normal. There was nothing to justify the assumption of an excessive stimulation beyond the point of neutralization (Pawlow's "overneutralization"). The emptying of the stomach was slightly delayed.

A series of experiments begun by von Noorden in the summer of 1890, and not yet completed, gave the following results:

A patient suffering from slight hyperacidity was given on ten consecutive days a test breakfast of 50 grammes biscuit, with either 400 c.c. of plain water or 400 c.c. Vals water (La Marquise, containing 0·7 per cent. $NaHCO_3$). Five minutes were allowed for eating the meal, and the stomach was emptied three-quarters of an hour later. The following results were observed:

Plain Water.		*Vals Water.*	
HCl.	Residue.	HCl.	Residue.
Per Cent.	c.c.	Per Cent.	c.c.
0·28	80	0·24	90
0·24	70	0·19	80
0·29	60	0·26	100
0·31	120	0·30	125
0·27	90	0·24	70
Average 0·278	85	0·246	93

The slight increase in residue counts for nothing, but it does seem as though there were some real, though small, decrease in the amount of hydrochloric acid in the chyme.

2. Mineral Waters taken before Food.

Accurate investigations have been made upon the effects of the "water cure" when the waters were taken some time before the test meal. Some of the observations extend over long periods.

The experiments may be divided into two groups :

1. The immediate effects on gastric digestion on days when the waters were taken and on the days when they were omitted.

2. The general results before, during, and after the whole "water cure," under practically constant conditions. The mineral waters were always analyzed before they were drunk on the test days.

(*a*) *Saline Waters.*

Meinel's (24) experiments on the immediate effects were carefully and accurately carried out. He first ascertained the state of the secreting functions after a simple test breakfast in a patient with slight atony of the stomach, then in three separate periods he gave respectively ¼ litre Wiesbaden Kochbrunnen (6·8 grammes NaCl per litre), Kochbrunnen containing CO_2, and Kissingen Rakoczy (5·8 grammes NaCl per litre) half an hour before the test breakfast under the ordinary spa conditions. It seemed that free HCl appeared more rapidly after taking NaCl water, that the total acidity was a little increased, and that the stomach emptied rather sooner ; this was most marked with Rakoczy water.

Maximum of Acidity in c.c. of Decinormal NaOH.	*Time in which Maximum was Attained.*	*Time of Emptying Stomach.*
Without Rakoczy water 65	45 minutes.	90 minutes.
With Rakoczy water .. 87	15 minutes.	75 minutes.

In another case of achylia gastrica no variations were observed.

Similar experiments were made by Bickel (25) partly on a dog (after Pawlow's operation), partly on a girl with a gastric fistula. He found that the mild saline waters stimulated the stomach to secrete slightly more HCl after the test meal.

Further investigations of this sort are wanted, for it is not yet known whether the mucous membrane of the stomach in disease is capable of giving different results, qualitatively or quantitatively, from the healthy mucosa. The first instructive work done on the general effects was that of Dapper (26) with Kissingen Rakoczy and Homburg Elizabeth waters. The subjects of his experiments were, without exception, suffering from

gastric disorders. After first carefully noting the condition and functions of the stomach, the usual quantity of water was taken in the ordinary way before breakfast for a period of a week. Thus the facts were observed before, during, and after the "water cure." The mineral water was analyzed on each of the test days.

In a long series of observations, Dapper describes seven cases where a subacidity due to gastric catarrh nevertheless yielded normal amounts of HCl. That this did not always occur, and that there were occasional mistakes, is not to be wondered at. Cases of achlorhydria and hypochlorhydria of nervous origin, or hypochlorhydria in phthisis, were practically not affected [*cf.* also Fischmann (28)]. Not only did these instances bear out the conclusions of practical experience, but numerous cases of hyperacidity (especially nervous hyperacidity and acid catarrh) reacted, as was generally held on empirical grounds, in the opposite direction, the high degree of acidity being lost. In chlorotic hyperacidity the results were disappointing.

The following table deals with seventeen cases of considerable hyperacidity benefited by saline water (Kissingen Rakoczy) :

	Hydrochloric Acid.		
	Maximum.	Minimum.	Average of Seventeen Cases.
	Per Cent.	Per Cent.	Per Cent.
Before treatment	0·35	0·29	0·33
After treatment	0·20	0·16	0·18

But in so refractory a condition as hyperacidity no one mineral water has been found a panacea. Dapper's work is open to the criticism that the number of investigations in particular patients was too small, for even in the same individual the acidity is wont to vary greatly from day to day [Ewald (27)].

Still, Dapper's conclusions are not based so much on the figures of individual stomach-washings as on the fact that the general tendency to increase or decrease remained constant in the favourable cases.

As a proof that the waters themselves possess certain powers, cases may be cited in which careful dieting made absolutely no difference, but directly the mineral water was added, decrease of acidity followed ; while, quite independently, clinical experience has constantly shown that in cases of hyperchlorhydria the administration of saline waters diminishes the acidity. This does not entirely agree with the researches of Meinel and Bickel (24, 25) as to the immediate effects of saline waters ; but the methods adopted were not the same. Further investigations may explain the apparent contradiction.

The question cannot well be one merely of stimulation and inhibition of acid secretion, or the exactly opposite effects in hypo- and hyperchlorhydria would not be seen. Probably much more complex changes take place in the mucosa involving exertion or suppression of many

functions. In the processes of cure the absence of certain normal products of the gastric mucous membrane, which has been so often described, must be taken into account. There is a need for further estimations on these lines.

(*b*) *Alkaline Waters.*

1. *Detailed Effects.*—Reichmann's researches (21) upon the direct effect of sodium bicarbonate, carried out by Meinel's methods (twenty-two experiments in four subjects), in which he administered large and small amounts of the alkali a definite time before meals, showed that this substance exerts but little effect on the secretion of hydrochloric acid.

Linossier and Lemoine (20), working with similar methods, found that sodium carbonate (5 grammes given an hour before meals) distinctly stimulated HCl secretion up to the point of neutralization, and perhaps beyond, for during the meal after the alkali had been given the amount of acid was abnormally high. We obtained similar results with Carlsbad waters, which, in spite of the small amount of Glauber salts, may be classed among the alkaline waters. The splendid work of the pioneers of gastro-chemical diagnosis (19, 29) gives no uniform results, perhaps because the methods were only in their infancy; but all agree that in some cases, whether in healthy subjects or in subacid gastritis, when Carlsbad waters were previously administered, the HCl and the total acid value was found to be slightly higher than normal after the digestion of the test meal was completed, and that the pepsin secretion and emptying of the stomach were slightly accelerated.

Bickel's (30) investigation represents the inauguration of more exact technique. Alkaline saline Carlsbad water does not affect the after-secretion in the stomach, while the simple alkaline waters—Vichy and Fachingen (5 and 3·6 grammes $NaHCO_3$ per litre)—have a slight stimulating effect on the healthy stomach.

Fischmann (28) gives the following table of the results of Carlsbad Mühlbrunnen (500 c.c.) on a case of severe hyperacidity (Meinel's method):

	In c.c. of $\frac{N}{10}$ *NaOH, at Periods of—*				
	15 Minutes.	30 Minutes.	45 Minutes.	60 Minutes.	75 Minutes.
Total acidity, after test breakfasts:					
Fore period: Plain water ..	28	55	60	55	60
500 c.c. Carlsbad Mühlbrunnen	35	60	75	65	67
After period: Plain water	22	40	55	55	52
Free HCl, under similar conditions:					
Fore period: Plain water	5	37	40	40	28
500 c.c. Carlsbad Mühlbrunnen	18	45	62	46	50
After period: Plain water	3	25	35	25	—

This case shows clearly the increase of acidity directly caused by the Carlsbad water; the after period shows a compensatory decrease of HCl.

2. *General Effects.*—Although the previous example of the action of the "water cure" on a particular act of digestion has some importance, the practical point for the physician is the general effect—namely, the state of digestion before and after the whole "cure."

Jaworski (19) stated that very often after prolonged periods of the Carlsbad waters (regular quantities every morning for four or six weeks) the specific functions of the stomach (secretion of HCl and ferments) were greatly hindered, and the mucous membrane through habit lost its power of responding to the stimulus; but Ewald (29), with whom we agree, in a series of similar experiments (10 persons), found that the HCl and ferments remain unaffected. There were considerable fluctuations, and the results were just as frequently above as below normal (21, 29).

Fischmann's results are stated in the following table:

Number of Experiment.	*Total Acidity (Averages only).*		
	Fore Period.	During "Cure."	After Period.
1	60	50	50
2	65	67	35
3	72	60	52
	Free HCl.		
1	49	43	35
2	40	46	27
3	52	42	36

The difference between the "cure" period and the fore period is unimportant, but the after period shows a marked decrease. Unfortunately, clinical facts, when placed against the experimental figures, show that, even if this decrease of hyperchlorhydria occurs at all, it is very transient. All practitioners, even the specialists, bewail the fact that the benefits of the waters are only symptomatic and temporary, and that for the prevention or permanent cure of hyperacidity they are powerless. Careful and patient dieting, prevention of constipation, and a generally healthy life are in most cases of infinitely more value (31, 32).

With alkaline, and particularly alkaline-saline waters, the experience of the simple salines is repeated. The variations in HCl may take place in either direction—decrease in hyperacidity and increase towards normal in subacidity (of catarrhal origin).

Fischmann's researches with ordinary amounts of mineral water as

usual simply bear out the clinical facts. The following table gives his results with 500 c.c. of Carlsbad Mühlbrunnen daily:

Number of Experiment.	*Total Acidity.*		
	Fore Period.	"Cure" Period.	After Period.
1	39	43	53
2	31	42	50
3	40	50	56
	Free HCl.		
1	12	23	34
2	8	24	26
3	22	31	36

It is unfortunate that there are so few adequate investigations of the general results of "water" cures on these lines, which are not difficult to follow, even for general practitioners.

Von Noorden, who long ago made similar researches in diabetes, has adapted his exhaustive and accurate methods to diseases of the stomach. In these experiments averages of three or four stomach washings were taken, forty minutes being allowed to elapse after the test breakfast (four Friedrichsdorf biscuits and 400 c.c. weak tea without sugar or milk).

Diagnosis.	*Spa.*	*Time.*	*Total Acidity.*		*Free HCl.*	
			Before.	After.	Before.	After.
		Weeks.				
Hyperchlorhydria nervosa (atony)	Vichy	4	0·40	0·42	0·31	0·30
Hyperchlorhydria (? ulcer)	Vichy	3	0·37	0·33	0·30	0·22
Hyperchlorhydria nervosa (without atony)	Neuenahr	4	0·41	0·39	0·25	0·29
Hyperchlorhydria nervosa (atony)	Carlsbad	4	0·39	0·28	0·27	0·16
Hyperchlorhydria (ulcer) ..	Carlsbad	4	0·42	0·30	0·29	0·11

These results are not quoted to illustrate any definite conclusion, but only to show the methods suitable for these investigations, where uniformity, length of time, and many series of cases are essential before material can be collected from which deductions of any value are likely to be made (*cf.* Saline Waters).

(*c*) *Bitter Waters.*

The direct effect of bitter waters is a decreased secretion of gastric juice, or, rather, of the specific ferments, for the stronger waters (Hunyadi Janos, 39·4 grammes sulphates per litre) can cause an increased secretion of water from the mucosa of the stomach [Bickel (30)].

General Effects.—Simon (33) made observations for periods of two or three weeks on healthy subjects and on cases of subacidity, giving every

morning 1 gramme of Glauber salts in 200 c.c. of water, ascertaining the acidity in the stomach by siphonage and analysis of the residue. With a single exception, no quantitative figures are given, and the number of separate investigations made on individual patients is so small that the following all-embracing conclusions he draws seem scarcely warranted :

" The chemical composition of the gastric juice is always altered in mucous gastritis, and invariably in the direction of an increase of acidity. No case showed subacidity. In atrophic catarrh, in symptomatic achlorhydria (phthisis), and in nervous disorders of the stomach, no good results were observed."

Gintl (34), using a similar method, found in a series of cases of subacidity that practically no increase of HCl occurred. Latkowski (35) describes an increase of acidity after taking Marienbad Kreuzbrunnen (4·8 grammes sulphates per litre) for long periods.

(*d*) *Calcium Waters.*

Clinical experience prompts us to suggest that in some cases the effects of calcium carbonate are more lasting than those of sodium carbonate. There is no experimental work of any value upon this question. Piatkowski (36) states that a course of four or five weeks of Krynica water (1·33 gramme $CaCO_3$ per litre) seems to lessen the hyperacidity in acid catarrh.

(*e*) *Sulphur Waters.*

Robin (37) considers that sulphur water given ten minutes before the test meal diminishes the acidity. This seems the only experimental research published. The work has been repeated by von Noorden in a case of nervous hyperacidity with the Weilbach sulphur spring (5·2 c.c. H_2S per litre) ; 400 c.c. of the sulphur water were taken half an hour before the test breakfast, and the stomach contents removed by siphonage forty minutes after the meal. Four consecutive washings-out gave an average total acidity of 91 (decinormal soda solution per 100 c.c. of gastric juice), and an average for HCl of 62. After taking the water for a fortnight four washings-out gave 73 and 42 respectively. This point requires further investigation.

Bain and Edgecumbe express the cautious opinion, based on clinical experience of the Harrogate old sulphur well, that " the water improves the appetite, stimulates the gastric functions, and may possibly supply material for the formation of HCl "; but give it as their belief that " the value of the water would be enhanced if it contained less hydrogen sulphide. This gas has been greatly overrated as a therapeutic agent, and the value of a health resort is hardly to be measured by the sulphuretted hydrogen content of its springs."

(*f*) *Chalybeate Waters.*

Scarcely any researches on iron-containing waters have been published, but we give the figures of some of our own experiments.

The good results of chalybeate waters in anæmia with hyper- or subacidity cannot be denied—perhaps, as in the case of saline waters, under given circumstances the acidity may be increased or diminished—but too much reliance must not be placed on a theory of merely local action on the stomach mucosa. It is no less likely that a general improvement in the organism as a whole tends to correct many defects of function.

The work of Buzdygan (38) relates only to iron-containing drugs, and does not even then give a very lucid explanation of their effects.

Clinical experience shows, at any rate, that chalybeate waters are not contra-indicated in the common form of dyspepsia with chlorosis.

The numerous digestive defects of this disease, whether hyper- or subacidity, atony or hyperæsthesia, are often rapidly improved by the chalybeate waters, which is more than can be said of the druggists' iron preparations, the organic and inorganic salts, the peptonates and albuminates, even the sulphate of iron waters (Levico, Roncegno) if drunk at home. All of these are unsuitable for chlorotics in whom disorders of the stomach and intestine are so constantly present.

At the spas, perhaps, the case is different. The following brief table shows how chlorotic hyperacidity can be improved by the regular chalybeate water "cure." All these cases were chlorotic girls with severe hyperæsthesia and hyperacidity of the stomach in whom five or six weeks at Marienbad or Franzenbad cured the chlorosis and improved the stomach troubles.

Name of Spa and Water.	*Fore Period: Two or Three Weeks before "Cure."*		*After Period: Three or Four Weeks after "Cure."*	
	Total Acidity.	Free HCl.	Total Acidity.	Free HCl.
1. Marienbad (Ambrosius water)	0·33	0·24	0·23	0·14
2. Franzenbad (chalybeate water)	0·42	0·30	0·25	0·11
3. Marienbad (Ambrosius water)	0·35	0·22	0·26	0·16

NOTE.—The figures are averages of two separate investigations in every case.

Van de Weyer and Wybauw (61) have quite recently published the results of three reliable investigations, from which they conclude—

1. The chalybeate waters influence favourably the absorption of albumin and carbohydrates in the intestine.

2. The tissue activities are increased: the total nitrogen output is augmented and the uric acid excretion diminished.

IV.—INFLUENCE OF MINERAL WATERS ON THE INTESTINE.

There are not sufficient data to furnish a study of the action of mineral waters upon all the various functions of the intestines.

Certain waters are known to stimulate the bowel to peristalsis and watery evacuations. This only bears on metabolism in so far as the

exchange of energy is increased, the composition of the fæces altered, or the assimilation of food and bacterial fermentation are interfered with.

A.—ASSIMILATION OF FOOD-STUFFS.

Very exaggerated ideas have arisen as to the amount of energy expended when by saline or bitter waters liquid evacuations are produced. In the statements about "metabolic activity" and its results in obesity at Homburg, Kissingen, and Marienbad, an important rôle is assigned to the diarrhœa, which is said to produce an increased output of oxidizable material.

At first sight there is a want of conviction about these theories, for mineral waters in ordinary amounts and under ordinary circumstances only serve to evacuate the normal contents of the bowels, which, apart from water and certain salts, do not include much nutriment. Exact investigations have shown this view to be justified alike by common sense and science.

1. *Plain Water.*

The mere bulk of water drunk (disregarding, perhaps, extremes in either direction) has no effect on the amount of absorption.

Dennig (39) found in some of his "thirst" experiments somewhat impaired assimilation as against unlimited water drinking, but this was rather a relative than an absolute reckoning. In two instances (Cases I. and IV.) the fæcal nitrogen was increased in the after period, especially as regards fat (in his first case 13·8 grammes of fat compared with 2·41). This he considered to be due to actual damage to the digestive organs from extreme want of water.

Case.	*Day of Experiment.*	*Disease.*	*Intake (Twenty-four Hours).*		*Output (Twenty-four Hours).*	
			Water.	Nitrogen.	Nitrogen.	Nitrogen.
			c.c.	Gm.	Gm.	Per Cent.
I.	1	Healthy subject	2,150	16·86	0·71	4·2
	2		530	13·12	0·90	6·8
	3		2,660	16·40	1·57	9·5
II.	1	Obesity	2,070	14·11	0·70	4·9
	2		380	8·39	0·83	9·9
	3		2,070	14·16	0·79	5·6
III.	1	Obesity	2,360	14·50	0·75	5·2
	2		550	12·66	0·73	5·8
	3		1,850	17·17	0·70	4·1
IV.	1	Obesity	2,415	20·37	0·70	3·4
	2		635	20·02	1·04	5·4
	3		2,415	20·37	1·67	8·2

Author.	Nitrogen.			Fat.			Mineral Waters.	Diagnosis.
	Daily Intake.	Daily Output.	Loss in per Cent.	Daily Intake.	Daily Output.	Loss in per Cent.		
	Gm.	Gm.		Gm.	Gm.			
Von Noorden (45A) ..	—	—	—	77·0	2·98	3·90	—	Obstipation.
	—	—	—	77·0	3·87	5·00	350 grammes Hunyadi Janos	
Katz (44)	17·14	0·76	4·0	125·0	2·30	1·80	—	Healthy.
	17·14	1·01	5·8	125·0	2·20	1·80	1050 c.c. Crodoquelle	
	17·14	1·02	5·5	125·0	2·10	1·70	—	
Dapper (45) ..	20·40	1·64	7·0	112·0	1·47	1·50	—	Healthy.
	20·76	1·89	8·0	112·0	2·80	3·00	300 c.c. Kissingen bitter water	
	19·94	1·84	9·0	112·0	4·10	4·00	500 c.c. Kissingen bitter water	
	20·92	1·76	4·0	112·0	1·48	1·50	—	
	16·75	1·62	9·0	137·0	5·30	4·00	—	Healthy.
	17·65	1·40	7·0	137·0	4·70	3·00	900 c.c. Rakoczy	
	17·20	1·41	8·0	137·0	2·60	2·00	—	
	14·86	1·00	6·7	40·0	2·90	7·00	—	Obesity.
	14·72	1·24	8·0	38·0	3·70	9·00	450–900 c.c. Rakoczy	
	14·90	1·28	8·0	36·0	4·40	10·00	450–900 c.c. Rakoczy + 200 c.c. Kissingen bitter water	
	15·00	0·93	6·0	40·0	3·08	7·00	—	Obesity.
	15·30	0·61	4·0	36·0	2·36	6·00	300–900 c.c. Rakoczy + 200 c.c. Kissingen bitter water	
	11·80	0·81	4·0	32·5	2·38	7·00	300 c.c. Rakoczy + 200 c.c. Kissingen bitter water	
	14·80	0·53	3·6	100·0	3·24	3·24	—	Obstipation and hyperchlorhydria.
	15·10	0·49	3·2	100·0	2·91	2·91	200 c.c. Rakoczy + 100 c.c. bitter water	
	13·00	—	—	175·0	13·00	7·50	—	Subacute gastric catarrh.
	13·00	—	—	175·0	12·00	7·00	600 c.c. Rakoczy	

Von Noorden (45A) ..	—	—	—	200·0	5·10	2·5	800 c.c. Homburg Elizabeth water	Gouty arthritis.
Dapper (45) ..	—	—	—	300·0	6·10	2·0	400 c.c. Homburg Elizabeth water	Gouty arthritis.
	29·40	3·00	10·0	242·0	20·90	8·7	—	Diabetes mellitus.
	29·80	2·80	9·5	249·0	26·80	10·7	600 c.c. Homburg Elizabeth water	
	30·10	3·26	10·8	261·0	27·20	10·4	800 c.c. Homburg Elizabeth water	
	17·53	1·00	5·7	115·0	1·50	1·3	—	Healthy.
	17·80	1·80	10·0	115·0	2·50	2·1	16 grammes Karlsbad Sprudel salts in 200 c.c. water	
	17·90	1·1	6·2	115·0	1·70	1·4	—	
Kraus (44)	—	—	—	208·0	9·24	4·6	—	Chronic intestinal catarrh with cystitis.
	—	—	—	214·0	9·10	4·2	400–600 c.c. Mühlbrunnen	
	—	—	—	214·0	17·31	8·1	700 c.c. Mühlbrunnen	
	—	—	—	215·0	8·26	3·8	—	Gout.
	—	—	—	194·0	11·60	6·0	—	
	—	—	—	194·0	6·30	3·2	500–600 c.c. Mühlbrunnen	Gastric ulcer; obstipation.
	—	—	—	227·0	5·30	2·3	—	
	—	—	—	236·0	7·40	3·1	300–700 c.c. Mühlbrunnen	
	—	—	—	249·0	3·15	1·7	—	
Ludwig (44) ..	32·30	1·31	4·07	—	—	—	—	Healthy.
	32·10	1·26	3·93	—	—	—	1,500 c.c. Mühlbrunnen	
	15·65	1·18	7·56	—	—	—	—	
	18·16	3·33	18·29	—	—	—	1,500 c.c. Mühlbrunnen	
Leva (44)	18·70	2·80	11·10	—	—	—	—	Healthy.
	18·70	2·23	11·90	—	—	—	400 c.c. Tarasp Lucius	
	18·70	1·86	10·00	—	—	—	—	
	18·70	2·27	12·10	—	—	—	800–1,000 c.c. Tarasp Lucius	
	18·70	1·94	10·30	—	—	—	—	
Ewald (44)	11·10	0·83	7·47	—	—	—	Levico water, 2 tablespoonfuls	Anæmia.
Schreiber (46) ..	17·95	1·21	6·70	106·8	4·03	3·8	—	Healthy (diarrhœa).
	19·84	1·43	7·20	101·9	7·33	7·1	Strong Levico water, 6 tablespoonfuls daily	
Henius (44)	11·50	1·02	8·80	—	—	—	—	Chlorosis.
	11·70	1·13	9·70	—	—	—	300–800 c.c. Val Sinestra	

Author.	Nitrogen.			Fat.			Mineral Waters.	Diagnosis.
	Daily Intake.	Daily Output.	Loss in per Cent.	Daily Intake.	Daily Output.	Loss in per Cent.		
	Gm.	Gm.		Gm.	Gm.			
Jacoby (44)	11·79	1·04	7·0	115·0	4·83	4·2	—	Obesity.
	17·30	2·05	11·8	138·0	8·75	6·3	125 c.c. Apenta	
	17·64	1·00	5·7	141·0	3·42	2·4	—	
Allard (44)	22·1	1·90	8·6	146·0	11·20	7·6	—	Diabetes mellitus.
	23·7	1·90	8·0	208·0	13·50	6·5	300 c.c. Mergentheim bitter water	
	24·0	2·10	8·7	209·0	11·60	5·5	—	
	13·3	1·66	12·5	223·0	13·20	6·0	—	Diabetes mellitus.
	14·5	1·16	8·0	121·0	12·60	10·0	300–450 Mergentheim bitter water	
	15·9	2·08	13·1	125·0	20·70	16·6	—	Diabetes mellitus.
	17·7	1·68	9·5	254·0	10·80	4·3	—	
	16·4	1·34	8·2	243·0	14·40	5·9	600–1,000 c.c. Mergentheim bitter water	
	16·1	2·87	17·9	249·0	15·40	6·2	—	Obesity.
	13·5	1·48	10·9	83·0	5·13	6·2	—	
	13·6	1·07	7·9	75·0	4·32	5·6	200 c.c. Mergentheim bitter water	
	12·2	1·27	10·0	45·0	5·38	11·9	—	
	12·0	0·78	6·5	44·0	3·60	8·2	200–300 Mergentheim bitter water	
	12·1	1·41	11·6	45·0	4·75	15·5	—	
Jacoangeli and Bonanni (47) ..	18·2	2·61	14·36	97·0	5·12	5·28	—	Healthy.
	18·2	2·45	13·48	97·0	2·19	2·26	1 litre Aqua Santa di Roma (alkaline)	
	18·2	2·30	12·66	—	—	—	—	Healthy.
	18·2	2·09	11·51	—	—	—	1 litre Aqua Santa di Roma (alkaline)	

Ruziczka (40) observed the effect of the addition of ½ litre of water to the ordinary diet. The diet was a constant one, consisting of :

	Dry Residue.	*Nitrogen.*	*Fat.*	*Carbo-hydrates.*	*Ash.*
	Per Cent.	Per Cent.	Per Cent.	Per Cent.	Per Cent.
First period ..	94·1	84·9	94·5	98·1	68·6
Second period ..	95·0	96·9	95·1	98·4	75·9

During the first period he drank ½ litre of water between meals, and during the second the same quantity with meals.

The variations lay within normal limits.

2. *Mineral Waters.*

The table on pp. 920-922 contains the results of various observations on absorption, with the amounts of mineral water commonly prescribed.[1]

This table, which comprises practically all the work on the subject, shows in every single case a slight increase in the excretion of proteins and fat (ether extract, " raw fat ") with the mineral water.

But the variations do not amount to much if the " cure " is continued for the customary period.

The nature of the proteins in severe diarrhœa has not been investigated. An analysis now being conducted in von Noorden's laboratory shows that the ratio between total nitrogen and ammonia nitrogen remains normal. In a case of gout examined to see whether the use of saline and sulphate waters produced any increase in the fæcal purins only negative results were obtained.

B.—BACTERIAL DECOMPOSITION.

The only method—and it is not a very satisfactory one—of determining whether mineral waters can arrest bacterial decomposition in the intestine is by estimating the ethereal sulphates in the urine. There is only a sparse literature on the subject. Hagentorn (48) reports that sodium bicarbonate has no effect on the amount of ethereal sulphates, while sodium citrate increases them slightly.

[1] The work of Anatoliew, Andrejew, Polissadow, Ratner, Chudsinsky, and Subow was not accessible in the original (41). According to the abstracts consulted mineral waters did not interfere with fat absorption. According to Coggi (42), sodium chloride retards fat absorption slightly when given in large amounts (20 grammes per diem). Smaller quantities have no effect. It appears that in the analysis of the fæces soaps were not taken into account.

Friedrichshall bitter water distinctly interfered with fat absorption in dogs [Vahlen (43)]. The results of London's otherwise very thorough researches could not be included in the table, as the fæces were not completely investigated (44). Brandenburg's results were very similar to Ludwig's and Kraus's (44).

Period.	*Average of Ethereal Sulphates.*	*Constant Diet plus—*
	Gm.	
1	0·2603	—
2	0·2791	1,080 c.c. soda water + 3·24 grammes sodium bicarbonate.
3	0·2701	1,080 c.c. soda water + 5·0 grammes sodium bicarbonate.
4	0·3149	1,080 c.c. soda water + 3·24 grammes sodium bicarbonate and 13·0 grammes sodium citrate.
5	0·3548	1,080 c.c. soda water + 13 grammes (additional) sodium citrate.
6	0·2630	—

Jawein (49) does not corroborate this ; 40 grammes of sodium citrate caused an increase just at first.

Number of Experiment.	*Normal Period.*		*Alkali Period.*		*Amount of Alkali.*
	Total Sulphates per Diem.	Ethereal Sulphates.	Total Sulphates.	Ethereal Sulphates.	
	Gm.	Gm.	Gm.	Gm.	
10	4·12	0·26	3·84	0·28	20 grammes $NaCo_3$ per diem.
9	4·26	0·24	3·91	0·26	20 grammes $NaCo_3$ per diem.
8	2·91	0·25	2·83	0·18	20 grammes sodium citrate per diem.
9	2·22	0·18	2·25	0·22	20 grammes sodium citrate per diem.
10	4·12	0·26	3·71	0·35	40 grammes sodium citrate per diem.
11	4·26	0·24	3·59	0·31	40 grammes sodium citrate per diem.

In three cases of severe diabetes [von Noorden] the daily administration of 15 grammes sodium bicarbonate had absolutely no effect on the amount of ethereal sulphates or on the intensity of the indican reaction. All three patients were kept on a constant diet without carbohydrates, and in addition took 5 grammes of sodium bicarbonate in the morning before breakfast, 5 grammes at bedtime, and 5 grammes in Seltzer water at intervals during the day.

Case.	*Sugar.*	*Ethereal Sulphates.*	*Sodium Bicarbonate.*
	Gm.	Gm.	Gm.
1	42·0	0·212	—
	39·7	0·222	15
2	12·1	0·198	—
	13·9	0·182	15
3	20·8	0·246	—
	16·9	0·260	15

Von Pfungen (50) obtained a somewhat better result with 4 grammes of sodium bicarbonate, approximately the amount that would be taken in mineral waters. The alkali was taken with the chief meals. The proportion of the combined to the preformed sulphates was not increased to more than 1 : 8, while the quotients 1 : 7 and 1 : 6 were frequently obtained. No figures are given dealing with the more important question of absolute values. In the same case (obstipation) the diarrhœa caused by a powerful aperient water sent the quotient down to 1 : 11 and 1 : 30. Obviously, there was an effect in this instance, but no absolute amounts were estimated. Gilbert and Dominici (51) produced the same result with purgative salts and water.

The first effect of calcium carbonate is also to increase the ethereal sulphates—25 to 50 grammes $CaCO_3$ [Kast (52)]. Von Noorden found that 25 grammes $CaCO_3$ per diem on a constant diet increased the ethereal sulphates from 0·133 gramme to 0·205 gramme ; but this, unlike Kast's results, is within the limits of normal variation. The following figures were obtained by Strauss (54) under von Noorden's direction :

Case.	*Ethereal Sulphates per Diem.*	
	Without $CaCO_3$.	With 20-25 Grammes $CaCO_3$.
	Gm.	Gm.
G.	0·285	0·325
B.	0·230	0·286

But these amounts of sodium and calcium are never used medicinally. Wendriner (55) found the indican decreased at first by drinking 700 c.c. Neuenahr water daily. The weak alkaline Aqua Santa di Roma has no effect on the ethereal sulphates (47) ; Batalin bitter water (8·83 per thousand $MgSO_4$ and 7·79 per thousand Na_2SO_4) increases them (56). The accompanying résumé of Porge's results with Marienbad Kreuzbrunnen (4·9 per thousand Na_2SO_4) is of interest (57) :

Case.	*Fore Period.*	*"Cure" Period.*	*After Period.*	*Mineral Water Daily during "Cure."*
	Gm.	Gm.	Gm.	
1	0·1467	0·1533	0·1545	500 c.c. Kreuzbrunnen.
2	0·1238	0·1260	0·1285	600 ,, ,,
3	0·1401	0·1447	0·1317	600 ,, ,,
4	0·1039	0·1259	0·1228	600 ,, ,,

The waters had no effect on a previously normal excretion of ethereal sulphates. As regards the total sulphates of the urine and fæces, the remarkable fact was ascertained that the absorptive and excretory effects of the sulphate are antagonistic to one another. In a case of "contracting kidney" on constant diet 600 grammes Homburg Elizabeth

water (11·6 grammes chlorides per litre) caused an increased nitrogen output, but at the same time a decrease of ethereal sulphates, whose amount (0·23 gramme) was abnormally high in proportion to the limited meat and increased milk consumption [von Noorden].

The intensity of the indican reaction fell with the ethereal sulphates.

	Nitrogen.	*Ethereal Sulphates.*	
	Gm.	Gm.	
Without mineral water ..	13·2	0·23	Average of 10 days.
With „ „ ..	16·0	0·16	„ 8 „

The following table is constructed from gastric cases investigated by Fischmann (28) :

Disease.	*Average of Ethereal Sulphates.*			*Constant Diet plus—*
	Fore Period.	"Cure" Period.	After Period.	
	Gm.	Gm.	Gm.	
Hyperchlorhydria and obstipation	0·373	0·150	0·076	500 c.c. Karlsbad Mühlbrunnen
Achlorhydria in anæmia ..	0·214	0·144	0·132	
Obstipation (stomach normal)	0·217	0·200	0·147	

In the absence of any reliable figures dealing with the iron waters, a table showing the action of the several iron salts, compiled from the works of Th. Mörner, may be appended (58). The quantities represent averages of individual periods :

Drug.	*Preformed Sulphates.*	*Ethereal Sulphates.*	*Ratio.*
	Gm.	Gm.	
None	3·723	0·348	1 : 10·7
Perchloride of iron (1 gramme)	3·423	0·341	1 : 10·0
Perchloride of iron (3 grammes)	3·498	0·322	1 : 10·8
None	3·925	0·351	1 : 11·1
Lactate of iron (3 grammes)	3·455	0·328	1 : 10·5

The ethereal sulphates were slightly diminished in this instance. Conti and Vitalli (59), however, were unable to discover such decrease with iron preparations.

Some further data of the effects of chalybeate waters are wanted, and also of those mineral waters generally which are by experience approved in diseases of the intestine.

Investigation of normal conditions promises no results of additional value. The cases which require investigation are those in which the ethereal sulphates, phenol, indican, and other evidences of bacterial decomposition of proteins reach an abnormally high point.

LITERATURE.

1. WINTER: De la concentration moléc. des liquides de l'organisme. Ar. P. **1896.** 114.—WINTER: De l'équilibre moléc. des humeurs. Ibid., 296.—KOEPPE: Ueber den osmot. Druck des Blutplasmas und die Bildung von Salzsäure im Magen. Ar. P. M. **62.** 567. 1896.

2. STRAUSS: Zur Funktion des Magens. XVIII. K. i. M. **1900.** 556.

3. PFEIFFER U. SOMMER: Ueber die Resorp. wässeriger Salzlösungen aus dem menschl. Magen. E. A. **43.** 93. 1899.

3A. STRAUSS: Ueber den osmot. Druck menschlicher Mageninhalte. Z. M. **57.** 19.

3B. SASAKI: Über den osmot. Druck des reinen Magensaftes. B. k. W. **1905.** 1386.

4. STRAUSS U. ROTH: Mechan. der Resorp. und Sekret. im menschl. Magen. Z. M. **37.** 144. 1899.

5. VON MERING: Ueber die Funktion des Magens. XII. K. i. M. **1893.** 471. —MORITZ: Ibid., 483.

6. BÖNNIGER: Ueber die Resorp. im Magen und die sog. Verdünnungssekretion. E. A. **50.** 76. 1903.

7. STRAUSS: Ueber die Bezieh. der Gefrierpunktserniedrigung von Mineralwässern zur Motilität und Sekretion des Magens. T. M. **1899.** 582.

8. KOSTKEWICZ: Die Gefrierpunktserniedrigung der versch. Mineralwässer. T. M. **1899.** 577.

9. VON NOORDEN: Ueber den Einfl. schwacher Kochsalzquellen auf den Stoffwechsel. P. 6. 1896.

10. PFEIFFER: Ueber die Resorp. wässeriger Lösungen. E. A. **48.** 439. 1902.

11. JUSTESEN: Ueber den Einfl. verschiedenartiger Nahrung auf die ClH-Sekretion und den osmot. Druck. im norm. menschl. Magen. Z. M. **42.** 451. 1901.

12. VON RZENTKOWSKI: Über das Schicksal von Salzlösungen im menschl. Magen. E. A. **51.** 289. 1904.—SOMMERFELD U. ROEDER: Ueber das physikal. Verhalten von Lösungen im menschl. Magen. B. k. W. **1904.** 1301.

12A. OTTO: Ueber das Verhalten von Salzlösungen im Magen. E. A. **52.** 370. 1905.—JUSTESEN: Ueber den Einfl. verschiedenartiger Nahrung auf die ClH-Sekret. und den osmot. Druck im norm. menschl. Magen. Z. M. **42.** 451, 1901.—PFEIFFER: Ueber das Verh. von Salzlösungen im Magen. E. A. **53.** 261. 1905.—STRAUSS: l. c. Nr. 3A.

13. KRESS: Bezieh. der Speichelsekret. zur Verdünnung des Mageninhaltes. E. A. **54.** 122. 1905.

13A. BICKEL: Exper. Untersuch. über den Magensaft. B. k. W. **1905.** 60.

14. QUINCKE: Ueber die Wirk. kohlensäurehal. Getränke. E. A. **7.** 101. 1877.—JAWORSKI: Über das Verhalten der Kohlensäure, etc., im menschl. Magen. Z. B. **20.** 234. 1884.—GILLESPIE: Carbonic Acid in Diseases of the Aliment. Tract. E. H. R. **4.** 1896.—PRAGER U. HENSEL: Beitr. zur Lehre von der menschl. Magenverdauung. D. Ar. M. **53.** 567. 1894.—KRIEGER: Aufenthaltsdauer von Flüssigkeiten im Magen. Diss., Erlangen, 1897.—PENTZOLDT: Wirk. der CO_2 auf die Magenverdauung. D. Ar. M. **73.** 200. 1902.

15. LIEBREICH: The Therap. Value of Alkaline Waters of the Vichy Type. B. M. J. **1902.** 11 October.

16. BECKER: Contrib. à la physiol. et à la pharmac. de la glande pancréatique. A. S. B. **2.** 433. 1893.

17. LERÈCHE: Rev. de Suisse rom. **1884.**—REICHMANN: Über den lokalen Einfl. des NaCl auf die Magensaftsekretion. E. A. **24.** 78. 1887.—WOLFF: Beitr. zur Kennt. der Einwirk. verschiedener Genuss- und Arzneimittel auf den menschl. Magensaft. Z. M. **16.** 222. 1889.—SCHÜLE: Sekret. und Motilität des Norm. Magens. Z. M. **28.** 461. 1895.—BÖNNIGER: Ueber den Einfl. des Kochsalzes auf die Magenverdauung. Mü. m. W. **1904.** 53.

18. BERGELL U. BICKEL: Physiol. Bedeut. der Radioaktivität der Mineralwässer. XXII. K. i. M. 1905. P. 157.

19. VON LEUBE: In Von Ziemssen's Handb. d. spez. Path. u. Ther. **7.**—JAWORSKI: Über die Wirk. des Karlsbader Thermalwassers auf die Magenfunktion. D. Ar. M. **37.** 1, 325. 1885.

20. Geigel u. Abend: Die Salzsäuresekret. bei Dyspepsia nervosa. Ar. p. A. **130.** 1. 1892.—Linossier et Lemoine: De l'action des alcalins sur la digest. gastrique. Ar. g. m. **1893.** I. 655. C. r. A. M. 28 Mars, 1893.—Du Mesnil: Ueber den Einfl. von Säuren und Alkalien auf die Azidität des Magensaftes Gesunder. D. m. W. **1892.** 1112.

20a. Ewald: Jb. L. M. **1892.** II. 163.

21. Reichmann: Ü. den direkten Einfl. des doppelkohlensauren Natrons auf die Magensaftsekretion. T. M. **1895.** 127.

22. Pawlow: The Work of the Digestive Organs. Translated. 1905.

23. Schüle: Sekret. und Motilität des gesunden Magens. Z. M. **29.** 49. 1896.

24. Meinel: Einfl. von Trinkkuren mit Kochsalzwässern auf die sekret. und motor. Tätigkeit des Magens. Z. d. p. T. **8.** 323. 1905.

25. Bickel: Über den Einfl. von Kochsalzthermen auf die Magensaftsekr. XXII. K. i. M. **1905.** 276.—Bickel: Über den Einfl. der Mineralwässer auf die sekretor. Magenfunktion. B. k. W. **1906.** Nr. 2.

26. Dapper: Ueber den Einfl. der Kochsalzquellen auf den Stoffw. des Menschen. Z. M. **30.** 371. 1896. See also N. k. A. H. 5. 1904.—Dapper: Ueber die Indikationen der schwachen Kochsalzquellen. XVII. K. i. M. **1899.** 355.

27. Ewald: Verdauungskrankh. und Balneologie. B. k. W. **1905.** Nr. 15.

28. Fischmann: Der Einfl. der Mineralwasser-Trinkkuren auf die sekret. Kraft des Magens. W. m. W. **1907.**

29. Sandberg u. Ewald: Ueber die Wirk. des Karlsbader Wassers auf die Magenfunktionen. C. m. W. **1888.** Nrs. 16, 18.—Spitzer: Zur Wirk. des Karlsbader Thermalwass. auf die Magenfunktionen. T. M. **1894.** 148.

30. Bickel: Lit. Nr. 25, 1906.

31. Strauss: Zur Frage der Ueberernährung bei der Diät in den Kurorten. D. M. Z. **1899.** Nrs. 37, 38.

32. von Noorden: Über Hyperazidität des Magensaftes und ihre Behandlung. Z. M. **53.** 1. 1904.

33. Simon: Ueber die Wirk. des Glaubersalzes auf die Magenfunktion. Z. M. **35.** 377. 1898.

34. Gintl: Über die Wirk. von Glaubersalzlösungen auf die Salzsäurereaktion. XVII. K. i. M. **1899.** 344.

35. Latkowski: Einfl. des Marienbader Wassers auf die motor. und sekret. Tätigkeit des Magens. W. k. W. **1899.** 706.

36. Piatkowski: Ueber die therap. Wirk. des Kalkes und insbesondere des Krynicaer Wassers auf den Verlauf der chron. Magenkrankh. W. k. W. **1898.** 10.

37. Robin: De traite. hydro-mineral des mal. de l'estomac. (Leç. sur les mal. de l'estomac.) 1903.

38. Buzdygan: Ueber den Einfl. des Eisens auf die Magensaftaussch. W. k. W. **1897.** 713.

39. Dennig: Die Bedeut. der Wasserzufuhr für den Stoffwechsel. Z. d. p. T. **1.** 281. 1898; **2.** 292. 1899.

40. Ruziczka: Ueber die Ausnutz. der Nährstoffe bei versch. Quantitäten des mit dem Mahle eingeführten Wassers. Ar. Hy. **45.** 409. 1902.

41. Andrejew: Einfl. des Kaukasischen Bitterwassers der Batalin'schen Quelle auf die Fettresorp. bei Gesunden.—Polissadow: Einfl. des Kaukasischen Bitterwassers der Batalin'schen Quelle auf den Stickstoffwechsel.—Anatoliew: Der Einfl. der Essentuky-Quelle Nr. 4 auf die Fettresorption. [This water is similar to Ems, with slightly increased amount of alkali.]—Chudsinsky: Der Einfl. der Essentuky-Quelle Nr. 4 auf den Stickstoffwechsel. 1897.—Subow: Einfl. der Essentuky-Quelle Nr. 4 auf die Fettresorp. bei Gesunden. Diss.—Ratner: Einfl. der Essentuky-Quelle Nr. 17 auf den Stickstoffw. All above are St. Petersb. Diss. 1897, in Russian.

42. Coggi: Act. du chlor. de sod. sur l'absorp. des Graisses. Ar. i. B. **23.** 315. 1897.

43. Vahlen: Ueber den Einfl. des Friedrichshaller Bitterwassers auf die Fettresorp. T. M. **12.** 130. 1898.

44. London, Brandenburg, Ludwig, Katz, Leva, Ewald, Henius, Allard: Nrs. 3, 5, 6, 9, 11, 12, 13, 14.—Kraus: Resorp. des Nahrungsfettes unter Einfl. des Karlsbader Mühlbrunnens. B. k. W. **1897.** Nr. 21.

45. Dapper: Stoffw. bei Entfettungskuren. Z. M. **23.** 113. 1893.—Dapper:

Ueber den Einfl. der Kochsalzquellen auf den Stoffw. des Menschen. Ibid. **30.** 371. 1896. See also N. k. A. H. 5. 1904.

45a. von Noorden: Reported by Dapper: Lit. Nr. 45 (1896, 1904).—von Noorden and Dapper: Concerning the Effects of Saline Waters on Metabolism. N. York. 1904.

46. Schreiber: Einfl. des Levikowassers auf den Stoffwechsel. Mü. m. W. **1902.** 1490.

47. Jacoangeli e Bonanni: L'azione sul ricambio materiale delle acque acidole alcaline (Aqua santa di Roma). Bu. R. **1896–97.** Nrs. 6, 7. Ma. **1897.** 655.

48. Hagentorn: Ueber den Einfl. des kohlensauren und zitronensauren Natriums auf die Aussch. der Säuren im Harn (in Stadelmann's Einfl. der Alkalien. 1890. P. 91).

49. Jawein: Über den Einfl. des CO_2NaH resp. zitronensauren Natriums auf den Stickstoffumsatz, etc. Z. M. **22.** 43. 1893.

50. von Pfungen: Zur Lehre von der Darmfäulnis der Eiweisskörper. Z. M. **19.** 118. 1892.

51. Gilbert et Dominici: L'antisep. intest. par la purgation. C. r. S. B. 21 December, **1895.**

52. Kast: Ueber die quantit. Bemessung der asept. Leistung des Magensaftes. Festschr. des Eppendorfer Krankenhauses. 1889. P. 1.

53. von Noorden: Ueber die Ausnutz. der Nahrung bei Magenkranken. Z. M. **17.** 525. 1890.

54. Strauss: Ueber die Einwirk. des kohlensauren Kalkes auf den menschl. Stoffwech. Z. M. **31.** 493. 1897.

55. Wendriner: Ueber den Einfl. des Neuenahrer Sprudels auf den Stoffwechsel. Z. d. p. T. **6.** 228. 1903.

56. Rosin: Der Einfl. des kaukasis. Bitterwassers der Batelin'schen Quelle auf die Menge der Aetherschwefelsäure im Harn. Diss. Petersb., 1897. (Ref. in Ma. **1897.** 575.)

57. Porges: Ueber die Sulfataussch. beim Gebrauch alkalisch-salinischer Quellen. D. m. W. **1905.** 542.

58. Mörner: Über die Wirkungsart der Eisenmittel. Z. p. C. **18.** 13. 1894.

59. Conti e Vitalli: Sui processi di putrefazioni intest. nella clorosi. An. c. F. **9.** 321. 1894. (Ref., Ma. **1894.** 358.)

60. Rheinboldt: Zur bakteriziden Wirk. radioaktiven Mineralwassers. B. k. W. **1906.** Nr. 20.—Heinsheimer: Über den Einfl. von Alkalien und Bittersalzen auf die Magensaftsekretion. M. K. **1906.** Nr. 24.—Das Experiment in der Balneologie. B. k. W. **1906.** Nr. 21.

61. de Weyer and Wybauw. Influence of Iron Water on Metabolism. Z. f. diät. Phys. Bd. X., p. 453.

V.—THE INFLUENCE OF MINERAL WATERS ON THE BLOOD.

A.—CONCENTRATION OF THE BLOOD.

1. Excess and Want of Water.

This subject has been zealously and profitably studied by the pioneers of biochemistry for many years past. The result of their researches is clear and instructive. In a healthy man, the drinking of an excessive amount of water at one time can in a short while (one-half to two hours) lower the density of the blood slightly, and the coagulability drops to ½ or even 1 per cent.; but this change is soon past, and the normal concentration regained [Lloyd-Jones, etc. (1), literature given by Glax (2)].

Leichtenstern allowed a healthy man to drink during three consecutive days a total amount of 21½ litres of distilled water without producing any marked change in the hæmoglobin (which was examined two or three times a day); but if the excretion of water is interfered with, as in cardiac or renal disease, this is not the case. Leichtenstern mentions a patient whose coefficient of excretion with ordinary quantities of water only averaged 1·106; when he drank 3,000 to 5,000 c.c. of distilled water for five days diuresis certainly increased, but still remained considerably less than the intake. The coefficient of excretion fell to 0·974, or about 12 per cent.

Author's Table of Effects in Kidney Disease.

Disease.	*Case.*	1,500 c.c. *Fluids.*		3,500 c.c. *Fluids.*	
		Average Diuresis.	Specific Gravity of Blood.	Average Diuresis.	Specific Gravity of Blood.
		c.c.		c.c.	
Chronic nephritis with dropsy	1	450	1047	950	1043
	2	700	1050	1,400	1045
	3	750	1050	1,250	1042
Chronic Nephritis without dropsy	1	1,200	1055	2,700	1055
	2	1,150	1054	2,400	1052
	3	1,300	1054	2,200	1050

These are a few selected instances.

There are many such determinations published. In a case of chronic parenchymatous nephritis, where the water taken was in excess of the diuresis, it was observed that the freezing-point of the blood fell within three days from −0·66° to −0·62°; or, in another case, within four days, from −0·60° to −0·57° [Kövesi and Roth-Schulz (3)].

A permanent hydræmia only appears in kidney disease after many days' indulgence—or misindulgence, rather—in excessive amounts of fluid. Single draughts leave the blood concentration untouched even in kidney disease. Steyrer (4) relates this fact of a case of parenchymatous nephritis where more than a litre of water was drunk at once.

Deficiency of water, on the contrary, has a much greater effect upon the blood density both in health and disease (5). In an anæmic patient undergoing the " thirst " cure (800 c.c. water per diem) the specific gravity of the blood rose from 1046 to 1056, and that of the serum from 1027 to 1033·5 [Salomon (5)].

2. Saline Mineral Waters and Solutions.

The strong saline aperient waters have a similar transitory effect (6). For their action on diffusion and secretion in the bowel, *vide* Pharmacology.

The increase of blood density does not always occur at the same

rate in every individual. Grawitz (6) records a rise of specific gravity from 1060 to 1062·5 fifteen minutes after taking sodium sulphate (15 grammes in a little water). In another case of obstipation 15 grammes magnesium sulphate in 50 c.c. of water produced no change in fifteen minutes, and after a further twenty minutes the specific gravity rose from 1050·8 to 1053·9, and for half an hour remained above 1052. In obstipation, this is only an interesting by-phenomenon, but in the treatment of dropsy it is an important factor. The free catharsis caused by strong aperient waters was highly esteemed by the older physicians for dropsies of all sorts, especially renal, and was, in fact, the recognised basis of treatment: one which, perhaps, the younger generation neglect, to their own no small loss.

The judicious use of purging in hydræmia and dropsy is a valuable remedy, and could fairly replace the now more popular "hot-air bath"; but the amount of water drunk must be strictly limited, for without this precaution purging, however drastic, will be of no avail.

So far only the fringe of a huge subject has been touched. There is much to be learnt of the effects of systematic purging on the blood, of the appropriate amounts, concentration, and kind of aperient waters, and of the state of the fæces as found by complete analysis.

Therapeutic results can only be obtained after diarrhœa has continued for some time. A single dose of concentrated salt solution has no effect on the blood. In one case Strauss (8) gave 10 grammes NaCl in 200 c.c. water without any change of freezing-point ($\Delta = -0{\cdot}61°$) or of electrical conductivity (106·7 S.E.). The salt content of the blood, which possesses a definite concentration maintained with great tenacity, and only yielding to very powerful influences, was also unaltered.

Cathartics used to be employed in pleural and peritoneal exudations, and effusions into joints. Unfortunately, it was found that these drugs required such a vigorous administration that the general health was apt to suffer serious damage; and this is the reason also why Schroth's "thirst" cure, which theoretically had a similar action, is now no longer in favour. In persistent effusions, well-regulated purging in conjunction with restriction of fluids might perhaps give better results by gradually increasing the concentration of the blood and causing resorption of the accumulated transudate and exudate.

Rothschild's (9) efforts to solve this problem were, unfortunately, based on the erroneous premise that weak hypertonic mineral waters—*e.g.*, NaCl and soda—could raise the molecular concentration of the blood, and so reverse the flow of fluid from the exudates back into the blood.

B.—MOLECULAR CONCENTRATION OF THE BLOOD.

The question of altering the blood density by drinking fluids becomes invested with fresh interest since physical chemistry has been applied to the study of the osmotic tension of mineral waters. Hopes began to be

awakened that in this direction might be found in the mineral waters of varying molecular concentration an easy and accurate means of influencing the osmotic tension of the blood, and with it the water and salt content of the tissues. Unfortunately these hopes were vain, for the previous sections will have made it clear that in the determination of molecular concentration we only possess a new measure for old values which, by other equally good measures, had been long ago accurately established, and were well known.

Following Dünschmann's (10) experiments on animals, Grube (11) studied the effects of Neuenahr Sprudel water, which is hypo-isotonic ($\Delta = 0{\cdot}095°$ to $0{\cdot}115°$). The investigations included a fore period of five days with ordinary diet, etc., a second period in which 1 litre of plain water was taken daily, and finally the main period of seventeen days, during which the same amount of Neuenahr Sprudel water was substituted (temperature 40° C.). The following results were obtained :

	Fore Period.	*Plain-Water Period.*	*Neuenahr Period.*
	Per Cent.	Per Cent.	Per Cent.
Osmotic tension of the blood ..	0·233	0·213	0·242
Water content of the blood	78·300	77·880	77·760

The blood was tested several times a day with Köppe's hæmatocrit.

Grube's conclusions are that by taking simple warm water regularly for a considerable time the osmotic tension is reduced, and there is also a decrease in the water content.

The intake of a warm mineral water under the same conditions produces an increase in osmotic tension and a decrease in the water content of the blood.

These changes appear at first to be only temporary, being present only during the few hours following the water-drinking. After regular administration of the mineral water they become of a more permanent character.

Engelmann (12) made a similar personal investigation with 500 c.c. of hyperisotonic Kreuznach water ($\Delta = -1{\cdot}03°$), using Köppe's hæmatocrit also. He records the following figures :

	Fore Period (Ten Days).	*Kreuznach Period (Nineteen Days).*
Osmotic tension in plasma (average) ..	−0·494°	−0·524°

Here, too, a marked increase occurred.

Seeing that by Strauss (13) and Grossmann (14) some doubt was thrown upon the value of the experiment, and especially upon the reliability of the hæmatocrit, Grube (15) repeated his investigations with Beckmann's apparatus. The accompanying table gives his findings :

	End of Fore Period.	*End of Water Period.*	*Seven Days Neuenahr Sprudel Water.*	*Fourteen Days Neuenahr Sprudel Water.*
Δ of blood-serum ..	−0·552°	−0·568°	−0·587°	−0·587°
Dry residue, per cent. ..	20·370	22·340	22·260	22·480
Ash, per cent.	0·713	0·782	1·002	1·006
Nitrogen in total blood, per cent.	3·220	3·510	3·490	3·520
Hæmoglobin	102·000	105·100	108·600	111·200
Erythrocytes	5,420,000	5,510,000	5,620,000	5,724,000

Grube sums up his results under three headings :

1. Decrease of water content.
2. Increase of ash.
3. Increase of osmotic tension.

Strauss and Grossmann obtained quite different results. Strauss found that in a patient suffering from gastric fistula, 500 c.c. of a 2 per cent. strongly hyperisotonic saline solution had no effect on the osmotic tension of the chyle (Δ after four hours remained at −0·54° C.).

Grossmann repeated on himself Grube's experiment with hypo-isotonic Neuenahr and hyperisotonic Salzschlirf Bonifacius water (Δ= −0·90°). However, he only drank 600 c.c., and examined not the blood but the serum, which is a more accurate method.

Date.	*Water and Period.*	Δ.	*NaCl.*	*Nitrogen.*	*Dry Residue.*	*Ash.*
			Per Cent.	Per Cent.	Per Cent.	Per Cent.
May 25	Beginning of experiment	−0·54°	0·558	1·18	9·35	0·92
June 15	After 20 days (Neuenahr water)	−0·54°	0·569	1·26	9·29	0·96
July 1	15 days' interval ..	−0·53°	0·560	1·22	9·52	0·98
July 20	After 20 days (Bonifacius water)	−0·54°	0·585	1·19	9·74	0·92

In this case, neither of the waters affected the osmotic tension. These apparent contradictions require explanation ; at first sight Grossmann's result seems more likely to be correct. Strauss (8) points out that the blood in health—disregarding the slight variations which Köppe (16) has shown to be physiological—maintains a wonderfully stable molecular concentration, and that such trifling interference as the drinking of large amounts of mineral water cannot produce any permanent effect on this important biophysical constant. It must be borne in mind, however, that observations made on the healthy subject do not necessarily hold good in disease, especially in those diseases which show pathological changes in the blood density ; possibly under these conditions the molecular concentration behaves somewhat after the fashion of the temperature. The investigation of this aspect of mineral waters is still only in its infancy.

C.—HÆMOPOIESIS.

Mineral waters have long enjoyed the reputation of promoting hæmopoiesis. By hæmopoiesis is understood an increase in the percentage of hæmoglobin and erythrocytes. Chalybeate waters, of course, are regarded as the most efficacious, but arsenical waters occupy a good second place.

1. The Effects of Iron in General.

We cannot discuss here the theories as to the action of iron. Von Noorden (17) has dealt with the subject from a general aspect, and has shown that the value of iron in anæmia depends less upon restoring to the system the actual amount of iron that is lacking than upon a direct chemical stimulation of the blood-forming organs. In this respect iron acts like arsenic and many other recognised remedies (*cf.* 17 and section Pharmacology in this book).

Many observers deny that iron has any curative powers in anæmia, especially chlorosis, but they attribute definite results of a far-reaching nature to the accompaniments of treatment, diet, hygiene, etc.

In many forms of secondary anæmia the doubt is justified; at least, good feeding and nursing play so large a part in the return to health that it is difficult to say that the iron administered has any share in the cure, and cases are common enough in which, through insufficient food, wretched surroundings, nervous depression, or some coexisting chronic disease, iron alone is useless.

Only when the cause is removed does the anæmia disappear; above all, iron is unavailing in those cases where the anæmia is due not to defective blood-formation, but to excessive blood-destruction, for iron only assists in blood-formation, and we know that in toxic and infective anæmias (pernicious anæmia included) many other factors than mere want of iron are at work.

The same holds good in the anæmia which follows septic or infectious fevers, where the exceptional demand made on the blood-forming organs during a protracted illness leaves them in a state of exhaustion or fatigue. Practical experience is very discouraging under these conditions. The general nutrition, which has been so sadly damaged, must first be made good before the blood can recover, and when the health as a whole is restored, the blood, as a rule, follows suit spontaneously; perhaps the use of iron hastens the course of events, but there is little proof of it. This is not true of chlorosis, a disease which seems to arise *sua sponte* even under apparently most favourable conditions of life. Although empirically it has been placed beyond dispute that iron does marked good in chlorosis, still the disease may in part be due to a debility of the blood-forming organs dependent upon an absence or deficiency of the physiological chemical impulses which normally proceed from the female generative organs—impulses which can be stimulated in other ways than by the exhibition of iron. So that lack of iron as the

determining factor in the production of chlorosis is a point as yet "not proven," and the same holds good of the "cure" of chlorosis by the administration of iron. Athough the theoretical action of iron may be questioned, its practical results in deficient states of the hæmoglobin or corpuscles have been convincingly demonstrated in ways that admit no argument (18).

2. Chalybeate Waters.

The effects of iron-containing waters have been more fully discussed in past times than of recent years (19).

We give a table of a few cases treated with 600 to 800 c.c. freshly drawn Schwalbach chalybeate water.[1]

TABLE OF HÆMOGLOBIN CONTENT OF THE BLOOD.

PERCENTAGES BY FLEISCHL'S OR GOWERS' HÆMOGLOBINOMETERS.

Case.	*Before Treatment.*	*After Two or Three Weeks.*	*Five to Six Weeks.*
1	66	72	81
2	51	69	73
3	60	62	75
4	58	65	80
5	70	80	95

The patients were all girls with uncomplicated chlorosis who had not been previously treated with iron; no changes were made in their diet or mode of living.

We give also a table of results obtained by Pfeiffer in Schwalbach:

Case.	*Before Treatment.*		*After Five Weeks "Rest Cure" at Schwalbach.*	
	Hæmoglobin.	Red Corpuscles.	Hæmoglobin.	Red Corpuscles.
1	60	4,500,000	80	4,550,000
2	72	4,500,000	80	—
3	50	—	75	—
4	80	4,025,000	98	4,500,000
5	60	4,000,000	85	—
6	75	4,100,000	95	—
7	60	4,500,000	85	—
8	80	—	92	—
9	83	—	90	—
10	40	—	75	—
11	28	3,600,000	38	—
12	60	4,100,000	80	5,000,000
13	65	4,300,000	85	—
14	50	4,000,000	60	—
15	62	4,000,000	82	4,500,000
16	70	4,500,000	100	—
17	65	—	100	—

[1] For changes in chalybeate waters due to bottling and storing, *cf.* von Noorden and Binz (20).

In these results, baths, fresh air, sun, and diet must be taken into account.

It has often been observed that the natural iron waters are more beneficial in chlorosis than the iron-containing drugs. The question is a complicated one; dilution, an empty stomach, and rapid absorption, all combine to make spa treatment more effective than any carried out at home. The chalybeate waters contain very little iron, perhaps only 0·025 to 0·03 gramme per day, while in the ordinary medicinal treatment often as much as 0·07 to 0·12 gramme per diem are administered.

3. Arsenic and Arsenical Waters.

Few mineral waters which contain arsenic without iron are used medicinally. Val Sinestra water is perhaps the only example; the iron it contains is a mere trace (less than 1 centigramme per litre), and the usual daily allowance of this water would not amount to more than 7 milligrammes of iron, an infinitesimal dose; at the same time, 3 to 4 milligrammes of arsenic would be taken, which is a relatively large quantity.

Henius (21) reported the following figures from three cases of chlorosis treated in von Noorden's clinic:

Case.	*Date.*	*Erythrocytes.*	*Hæmoglobin.*
1	October 25, 1903	3,500,000	40
	November 13, 1903	3,900,000	75
2	October 25, 1903	3,450,000	50
	November 20, 1903	4,430,000	70
3	October 8, 1903	3,120,000	55
	October 25, 1903	4,200,000	80

For the effects of pharmaceutical preparations of arsenic *cf.* section Pharmacology and reference 17.

Mineral waters which contain both arsenic and iron (especially sulphate of iron) are rapidly growing in favour. Clinically, their value is indisputable, but so far it has not been possible to estimate separately the effect of the arsenic or the iron. In certain diseases of the hæmopoietic system, such as pernicious anæmia and leuchæmia, it has been thoroughly established that iron alone is useless, while with arsenic—at least, in some cases—good results are obtainable. The iron and arsenical waters are employed at home and in hospitals quite as much as at the spas; they do not seem to deteriorate when bottled like the carbonate of iron waters.

The following table gives a brief résumé of published results. All the cases are simple except Ewald's (hysteria and anæmia) and Liermberger's (anchylostomiasis):

Observer.	Before Treatment.		After Treatment.		Duration in Weeks.	Waters.
	Hæmoglobin.	Corpuscles.	Hæmoglobin.	Corpuscles.		
Ewald and Dronke (22)	Per Cent. 82	5,120,000	82	5,400,000	9	Levico.
Reinl (19) ..	45	3,597,000	102	4,960,000	6	Levico.
	52	3,797,000	92	5,523,000	5	
	28	2,230,000	95	3,200,000	5	
Von Noorden	45	4,000,000	75	4,700,000	5	Roncegno.
	55	3,900,000	85	4,800,000	6	
	45	3,500,000	85	4,750,000	5	
	68	4,500,000	95	4,550,000	5	
Liermberger (23)	18	1,454,000	61	4,600,000	13	Levico.
	17	1,550,000	91	4,200,000	14	
	30	2,150,000	82	5,070,000	12	
	20	1,562,000	66	3,837,000	15	
	35	3,375,000	90	4,766,000	15	

This subject has hitherto been somewhat neglected, although recent advances in the methods of clinical research might throw fresh light on the complex problem of the combined action of arsenic and iron.

D.—ALKALINITY OF THE BLOOD.

It is impossible to consider the effects of alkalis on the blood and intermediate processes of metabolism separately from those on the urine, so that many facts which might figure in this section will be found in their proper place under Urine.

Very little is known of these effects of alkalis in general, and much less when we deal only with the amounts and varieties of alkalis found in medicinal waters. Hardly any mineral waters contain more than 5 grammes $NaHCO_2$ per litre (Vals Madeleine, Vichy Celestin, and Grand Grille Passuger Ulricus) ; in the next rank are Biliner (4·6 grammes) and Fachinger (3·6 grammes) ; then Carlsbad, Marienbad, Franzensbad, Salzbrunn, Oberbrunnen, Ems, La Bourboule, Royat, Neuenahr, with considerably less alkali. Changes of alkalinity in the blood itself cannot be demonstrated (24).

Freudberg (25) found in man a very slight and transitory increase of alkalinity by Sahli's method. Foderà and Ragona (26) observed a trifling increase after very large amounts of alkali (1 gramme per kilogramme body-weight), but this only occurred on a vegetable, and not a meat diet. Pergami (27) corroborates this for rabbits. We should not attach so much importance to these changes occurring in vegetarians, for Walter (28) has already shown that the chemical reaction of their blood is much more liable to variation.

Burmin (29), who reports an isolated case of increased blood alkalinity

from drinking daily one bottle of Kronenquelle (= 164 to 182 milligrammes NaOH), based on a single estimation, cannot be credited with having settled the question once and for all. In fact, all the variations recorded are very small, while all the methods employed are inexact.

The continuous administration of alkalis, especially sodium, lithium, potassium, and calcium, can produce changes of reaction in the blood and tissues, consisting chiefly of variations in the inorganic composition, which are not without some bearing on the intermediate processes of metabolism, possibly of a catalytic nature affecting disintegration and oxidation.

There has in times past been a great talk about " increased metabolism," " stimulation of the processes of oxidation," and the " alterative effects," due to mineral waters, in proof of which is quoted the actual decrease of uric acid, oxalic acid, and the neutral sulphates in the urine. These theories seemed to explain the therapeutic results of the " water cures " in obesity, diabetes, and gout.

As a matter of fact, many chemical processes may take place in a test-tube, according as more or less alkali is added. The solubility of urates depends to a great extent on the alkali or salts in the solvent. Sodium carbonate, even in small amount, retards the diastase fermentation of glycogen [Gans (30)]. Upon this fact the observer builds up a magnificent theory that in diabetes the administration of soda will act similarly, and delay the converting of liver glycogen into sugar, thus giving time for the free sugar already formed from the glycogen to be oxidized before fresh sugar is poured in, so that the blood is protected from an excess of sugar. Although this theory meets with little encouragement clinically, an explanation of what ought to happen is ready to hand. The chemistry of the test-tube does not coincide with the phenomena of biology ; some links in the chain of evidence are too often lacking. We do not know the temporary resting-places, nor the ultimate destinations, of the alkalis consumed, while they are circulating through the various organs or are eventually retained in the organism.

At what spot in the tissues does the alkali absorbed by the stomach come to the full development of its innate properties ?

The organism still guards this secret in diabetes, in spite of the most searching examinations of the blood and tissues, sometimes with and sometimes without the previous administration of alkalis [Magnus-Levy (31)]. The amount of fixed alkali is practically the same in either case.

From former analyses, and the more recent work of Abderhalden (32) and Rumpf and Dennstedt (33), it is well known how variable are the proportions of inorganic constituents or bases in the blood and organs of persons who have died of disease. The alkalis in particular seem to have no definite proportions ; their relations to nutrition and disease are most uncertain and inconstant. Inorganic substances do not obey the same strict rules of intake and output which govern nitrogen and the mineral acids. The taking of one alkali may affect the output of another, so that the relative composition of the body as regards alkalis is for the time being altered.

Von Noorden (34), in 1893, gave a girl suffering from chronic articular rheumatism about a litre of milk daily, with 5 grammes CaCl and 5 grammes $CaNO_3$, during a period of three weeks. During this time more than 12 grammes of potassium and 20 grammes of calcium were retained in the tissues, while large amounts of sodium salts were excreted. That the calcium contained in certain food-stuffs can accumulate in large quantities has been frequently shown.

There can be no question that in the selection and administration of alkalis we possess a powerful means of working great changes in the alkaline constitution of the body. The aims we have in view, the processes we set in operation, and the results we achieve, are all profoundly obscure, and even if we could unravel the mysteries of health, they might still baffle us in disease.

Inorganic changes must surely be of great importance in many of the processes of metabolism, but our clinical and experimental data are confined only to an insignificant portion of the whole. Investigations have been attempted upon the calcium exchange in diseases of joints and bone, calcium and magnesium loss in diabetic acidosis, the inorganic output in chronic infections (" demineralization " in tuberculosis), and in quite recent times upon the " chloride balance " in kidney disease. At present there is, perhaps, a tendency to overestimate the therapeutic capabilities of our scanty knowledge, but we are opening up new and unexpected fields of research, in which one day a fruitful harvest may be reaped.

The penetration of the dark by-paths of mineral metabolism will benefit balneology above everything. The knowledge that by systematic incorporation of certain bases or acids into the blood we can affect certain tissues or control certain biochemical processes will place the therapeutic effects of mineral waters on a secure and scientific foundation.

The very number of mineral waters and the diversity of their composition offer us in pleasant and handy forms fixed combinations which may be made to fulfil all our requirements and comply with our nicest calculations. Many problems in balneotherapy might be solved from this standpoint, and the cautiously sceptical theorist may one day stand ashamed before the acumen of the empiric.

LITERATURE.

1. Nasse: Ueber den Einfl. der Nahrung auf das Blut. 1850.—Leichtenstern: Ueber den Hämoglobingeh. des Blutes. 1878.—Schwendter: Die Beeinflussung der Blutkonzentr. durch den Flüssigkeitsgehalt der Kost. Diss. Bern, 1888.—Schmalz: Unters. des spezifis. Gewichts des menschl. Blutes. D. Ar. M. **47.** 145. 1891.—Tietze: Ueber den Hämoglobingeh. des Blutes unter verschied. Einflüssen. Diss. Erlangen, 1880.—Oertel: Allge. Ther. der Kreislaufsstörungen. 1891. P. 57.—Jones: On the Variations in the Spec. Grav. of the Blood in Health. J. P. **8.** 1. 1887.

2. Glax: Balneologie. **1.** 27. 1897.

3. Kövesi u. Roth-Schulz: Ueber die Niereninsuffizienz bei Nephritiden. P. 91. 1904.

4. Steyrer: Ueber die osmot. Analyse des Harns. Be. P. P. **2.** 231. 1902.

5. Dennig: Die Bedeut. der Wasserzufuhr für den Stoffwechsel. Z. d. p. T. **1.** 281. 1898; **2.** 292. 1899.—Salomon: Ueber Durstkuren, besonders bei Fettleibigkeit, N. k. A., H. 6. 1905.—von Noorden and Salomon: Diseases of Metab. and Nutrition. **6.** N. York, 1905.

6. Viola, cit. by Hamburger: Osmot. Druck und Jonenlehre. **1.** 505. 1902.—Hay: The Action of Saline Cathartics. J. A. and P. **1882.** 243.—Grawitz: Klin.-exper. Blutuntersuch. Z. M. **22.** 411. 1893.

7. Hay: On the Use of Concentrated Sol. of Saline Cathartics in Dropsy. L. **1883.** Vol. I. 678.

8. Strauss: Ueber den Einfl. von Trinkkuren auf die Zusammensetz. der Blutflüssigkeit des Menschen. Z. d. p. T. **7.** 388. 1904.

9. Rothschild: Zur Nachbehandlung pleuritischer Exsudate. T. G. **1903.** 160.

10. Dünschmann: Einfl. des Salzgeh. der Trinkquellen auf die Blutbeschaffenheit. Z. M. **44.** 91. 1902.

11. Grube: Ueber den Einfl. der Mineralwässer auf das Blut. Z. d. p. T. **6.** 334. 1903.

12. Engelmann: Einfl. der Kreuznacher Quelle auf die Beschaffenheit des Blutes. D. M.-Z. **1902.** 441.

13. Strauss: Ueber osmot. und chem. Vorgänge am menschl. Chylus. D. m. W. **1902.** 664.

14. Grossmann: Ueber den Einfl. von Trinkkuren mit Mineralwässern auf den osmot. Druck des menschl. Blutes. D. m. W. **1903.** 276.

15. Grube: Ueber den Einfl. der Mineralwässer auf das Blut. Z. d. p. T. **7.** 255. 1904.

16. Köppe: Physikal. Chem. in der Medizin. 1900.

17. von Noorden: Die Bleichsucht, P. 151, in Nothnagel's Handb. 1897.

18. Bauhölzer: Über die therap. Erfolge des Ferratins. C. i. M. **1894.** 73.—Stockman: Treatment of Chlorosis by Iron and other Drugs. B. M. J. **1893.** 29 April.—Biernacki: Ueber die Leistungsfähigkeit der Eisentherapie. W. m. W. **1903.** Nrs. 18-20.—Romberg: Über Chlorose und ihre Behandlung. B. k. W. **1897.** Nr. 25.—Schauman u. Willebrand: Bemerk. über die Blutregeneration bei Chlorose. B. k. W. **1899.** Nr. 1.—Laache: Die Anämie. 1883.

19. Scherpf: Hämoglobinmangel und sein Verhalten während einer Stahlkur. Z. M. **4.** 575. 1882.—Reinl: Über die Heilwirk. von Mineralwasserkuren bei anämischen Zuständen. Z. H. **9. 785.** 1888.—Stifler: Die Wirk. einfacher Stahlquellen bei Anämie auf Grund von Blutkörperchenzählungen. B. k. W. **1882.** Nr. 16.—Wasowicz: Ueber die Wirk. des Krynica-Eisenwassers bei Chlorose und Anämie. Gaz. lekarska. **1900.** Nrs. 20 and 21.—Siegfried: Ueber die Wirk. der Eisenquelle in Rippoldsau. XIII. K. i. M. P. 175. **1895.**

20. von Noorden: l. c., Nr. 17. P. 161.—Binz: Der Gehalt. der natürl. Eisenwässer an gelöstem Eisen. D. m. W. **1901.** Nr. 14.

21. Henius: Ueber das arsenhaltige Wasser von Val sinestra und über seine Wirk. auf den Stoffwech. D. m. W. **1904.** 949.

22. Ewald u. Dronke: Ueber den Verlauf des Stoffwech. bei längerem Gebrauch des Levico-Arsen-Eisenwassers. B. k. W. **1892.** Nrs. 19 and 20.

23. Liermberger: Zur Behandl. der Anchylostomiasis und der Tropenanämie. B. k. W. **1905.** Nr. 14.

24. Buchheim: Arzneimittellehre. 1878.

25. Freudberg: Ueber den Einfl. von Säuren und Alkalien auf die Alkaleszenz des menschl. Blutes und auf die Reaktion des Harns. Ar. p. A. **125.** 566. 1891.

26. Foderà e Ragona: Studie sull' alcalescenzia del sangue. A. F. **5.** Mai. 1897.

27. Pergami: Azione delle sostanze alcaline somministrate per la via della stomaco sull' alcalescenzo del sangue. Ann. di farmacoter. **1899.** 293.

28. Walter: Wirk. der Säuren den auf tieris. Organismus. E. A. **7.** 148. 1877.

29. Burmin: Alkales. des Blutes bei einigen patholog. Zuständen. Z. M. **39.** 365. 1900.

30. Gans: Ueber den Einfl. von Salzlösungen auf die Umbildungsgeschwindigkeit des Glykogens in Zucker. XIV. K. i. M. **1896.** 449.

31. Magnus-Levy: Die Oxybuttersäure. E. A. **42.** 149. 1899.—Über Azidosis im Diab. mell. Ibid. **45.** 389. 1901.

32. Abderhalden: Zur quantit. vergleichenden Analyse des Blutes. Z. p. C. **25.** 65. 1898.

33. Rumpf u. Dennstedt: Über die chem. Zusammensetz. des Blutes. Z. M. **58.** 84. 1905.

34. Bunge: Lehrb. der phys. und path. Chemie. 1889.—Beckmann: Über den Einfl. des kohlensauren und zitronensauren Natrons auf die Aussch. der Alkalien; in Stadelmann's Einfl. der Alkalien auf den Stoffwechsel. 1890. P. 52.—Strauss: Ueber die Einwirk. des kohlensauren Kalkes auf den menschl. Stoffwechsel. Z. M. **31.** 492. 1897.—Herxheimer: Ueber die therap. Verwendung des Kalkbrotes. B. k. W. **1897.** Nr. 20.

VI.—THE INFLUENCE OF MINERAL WATERS ON THE URINE.

A.—DIURESIS AND EXCRETION OF SALTS.

One of the oldest and most highly extolled properties of mineral waters is their power of promoting diuresis. There is nothing peculiar to the mineral waters in this, the drinking of any water stimulates the kidney to get rid of the additional water in order to restore the normal concentration of the blood.

The question is simply whether the presence of certain inorganic substances dissolved in the water increases or retards this important renal function. In the healthy subject many investigations have been made. Most of them "had the unexpected result that the mineral water in question stimulated diuresis marvellously."

The wearisome literature has been admirably surveyed by Glax (1).

In general it is perfectly true that mineral waters have a greater diuretic effect than plain water, but the effect is very transient, lasting only a quarter to half an hour. This diuresis depends chiefly on two factors:

1. The more rapid emptying of the stomach into the intestines, which, as has already been shown, is largely a question of the degree of molecular concentration of the contents. The great majority of mineral waters in use have a low concentration ($\Delta = -0{\cdot}3°$ to $-0{\cdot}4°$).

The temperature, too, counts for something. Hot drinks, perhaps, stimulate peristalsis slightly; but in reality the temperature at which a hot drink reaches the stomach is not very far removed from that of the blood. Water at a temperature of 55° C. can only be sipped, and in this way it loses some of its heat during swallowing.

But with cold drinks the case is different. We cannot apply any sort of scale to the problem, but it can be accepted as certain that very cold drinks, like ice-water, remain in the stomach much longer than warm drinks—at least, in many people. Habit modifies this, however. Badt and three companions worked this out upon themselves in von Noorden's clinic by the method described previously. In three of them the drinking of ice-cold tea before breakfast caused delayed emptying of the stomach; in the fourth no difference could be detected. It was, perhaps, not a mere question of chance that this man had been accustomed from his infancy to iced beverages. Unfortunately, no measure

was taken of the diuresis. The amount drunk was 600 c.c., and the stomach was emptied after forty minutes.

Case.	*Temperature of Tea* = 50°.	*Temperature of Tea* = 0°.
	Residue.	Residue.
	c.c.	c.c.
1	120	320
2	60	340
3	90	200
4	140	150

Also, the percentage of CO_2 in the mineral water, which increases the motility of the stomach, falls at the lower temperature.

As soon as the water reaches the small intestine absorption begins, and proceeds so rapidly that at 10 to 12 inches from the pylorus it is difficult to say whether the contents of the gut are fluid or solid.

2. The second factor is very largely a question of the time which it takes certain diuretic substances contained in the water to reach and stimulate the renal epithelium. There are many organic (caffeine and theobromine) and inorganic substances (sodium chloride, Glauber salts, etc.) which, when introduced into the blood, come into contact with the epithelium of the glomeruli, and stimulate the secretion of water [Magnus-Levy and Loewi (2)]. The latter group enter largely into the composition of mineral waters. Pharmacological experiments in animals are throwing much light on the facts of human physiology and pathology. It would be a very valuable line of research to work out these experiments completely in man both in health and disease.

It will be no simple task to compare the effects of all the various inorganic substances and mineral waters under every physiological and pathological condition, and we cannot apply the convincing tests of intravenous infusion or the removal of one kidney to ascertain the rate of emptying the stomach and variations in absorption through the surviving kidney. But these investigations must be made with as great care and accuracy as those on nitrogenous equilibrium. The diet must be absolutely constant, and administered in exactly equal quantities. The salts actually or potentially contained in the numerous by-products of the food and the tissues must be estimated as carefully as those contained in the mineral water, for they, too, can affect the renal epithelium, and every variation in their quantity, quality, or concentration will obscure the action of the test substance and vitiate the results.

Even if such strict methods can be adopted, we can scarcely hope to obtain sufficiently exact data to enable us to standardize the particular salts and mineral waters according to their effect upon the human kidney in health and disease.

The important point in treatment is not merely to what extent and at what rate the kidneys excrete the mineral water—that is evidently

the least part of the problem. The chief thing is whether this general stimulation of diuresis excites the elimination of other substances (water, salts, organic products of metabolism, drugs, poisons, etc.).

Many detailed facts are known—for example, the temporary increase of urea output, erroneously regarded as a sign of increased protein disintegration, which is relatively the greater, owing to the early appearance of the diuresis; the similar output of uric acid, where, however, the admixture of neutral or alkaline salts with the water makes a considerable difference; the occasional marked increase in water and sodium chloride excretion in kidney disease caused by the administration of a few grammes of sodium chloride [Mohr (4)]; diminution of the phosphates when the reaction of the urine is rendered alkaline, particularly by calcium carbonate (5).

Truly the study of the exchange of inorganic material promises to open up, not new country merely, but a fresh continent.

The insignificance of our total knowledge of the metabolism of mineral substances and its variations is made only too apparent by the careful and complete survey which Neuberg and Albu (6) have published.

Very valuable researches have been carried out with some substances—for instance, the effect has been determined of large doses of the carbonate or organic salts of sodium upon the excretion of acids and bases in health [Stadelmann, (7)] and in disease, *e.g.*, diabetes mellitus [Stadelmann, Magnus-Levy, Gerhardt, and Schlesinger (7A)].

With mineral waters, or corresponding solutions of salts, no such investigations have been performed.

The whole problem of water excretion by the kidney requires to be worked out *ab initio* with new methods and modern accuracy.

Not only must the relation of food-stuffs to the urine be minutely investigated, but all the attendant circumstances of water excretion—such as temperature and moisture of the surrounding air, muscle work and muscle rest, with all the secondary effects on the disposal of the water retained in the system—must be determined. The antiquated jargon of balneology about certain waters promoting diuresis is nonsense from beginning to end; only a series of comparable experiments can yield that scientific knowledge upon which treatment can be securely founded.

The problem is twofold:

1. Is the increased secretion of urine set up by water and its inorganic constituents merely temporary, both as regards rate and quantity, in man, as experiments have proved it to be in animals? If so, there may be a similar period of reaction and decrease afterwards.

2. Is the total water and salts balance affected, so that after prolonged administration of mineral waters the system becomes actually richer or poorer in water and salts, and what particular minerals possess this power of varying the chemical constitution?

After these problems have been solved, there remains the still harder task of apportioning to the various tissues their share in the whole process. Clinical experience certainly provides a point to start from as to when and where such effects occur, and when and where we may avail ourselves

of them, but these empirical beginnings cannot yet be reduced to scientific order. We see now that, under the old catch-phrase "our mineral waters promote diuresis," there lies unsolved a great store of interesting and complex problems; but a task of vast magnitude faces us when we attempt to grapple with the therapeutic achievements of balneology, and submit them to the impartial tests of scientific inquiry.

B.—REACTION OF THE URINE.

One of the chief aims of hydrotherapy is to control the reaction of the urine, with the object of decreasing or neutralizing its acidity; the slight increase of acidity caused by alkali-free waters which contain CO_2 is only a matter of conjecture. All reports upon change of reaction in the urine are to be accepted with considerable caution, for the simultaneous presence of weak acids and weak bases interferes with the observation of the reaction.

None of the present methods are wholly free from objections. Auerbach and Friedenthal's (9) process seems the best, and by it we find that normal urine, even if it turns litmus distinctly red, may actually be less acid than one which does not act so markedly upon litmus. This difficulty of determination is much less if weak bases predominate in the urine, and disappears when the reaction is distinctly alkaline.

By drinking large quantities of plain water, or by increase in the flow of urine, the faintly acid components of the urine may be masked by the faintly alkaline, and the reaction may become almost or quite alkaline [Rudel (10)]; but Haussmann (11) has shown that, in spite of this relative decrease of acidity, the total acid output may be actually increased. It is very easy to abolish the acid reaction of the urine by taking alkalis, although the amounts required vary greatly in different individuals.

In many instances a single bottle of Fachingen or Vichy (4·8 to 7·3 grammes sodium bicarbonate per litre), drunk at intervals during the day, will give the whole of the urine passed an alkaline reaction [Klemperer (12)]; in other cases there was only a natural decrease of acidity, such as always follows the chief meals of the day (13), and depends on the movement of acid ions into the stomach, sometimes actually rendering the urine alkaline; in yet others again, the taking of such alkalis had no effect at all, and 10 to 12 grammes of sodium carbonate were required to make the urine alkaline.

The most important aspect of the urine reaction is in relation to the formation of uric acid concretions in the urinary tract. Pfeifer (14) was the first to prove that the urine passing through a "uric acid filter" under certain conditions gave up its uric acid, and under others took up uric acid from the filter. Posner and Goldenberg (15) have made careful researches into the power which various mineral waters possess of dissolving uric acid in the urine. After the administration of certain waters (600 to 1,000 c.c. per diem) the urine usually acquired this solvent

property, so that out of about ½ gramme of uric acid added, a few centigrammes—sometimes even 1 to 1·5 decigrammes—were dissolved within twenty-four hours. Without the administration of alkaline waters the addition of uric acid crystals as a rule causes a further precipitation of uric acid. Posner and Goldenberg disagree with Pfeiffer, and state that the after-effect is not lasting. At the end of the water cure the power of the urine to dissolve uric acid disappears at once.

Such " alkalized " urine, however, is able to dissolve some five or ten times more of the chemically pure uric acid than of the natural concretions broken or powdered up, for the organic constituents of the concretion prevent the thorough penetration of the fluid. It is evident from these and subsequent experiments that it is the reaction rather than the quantity of urine which determines this solvent power (16). Klemperer (14) demonstrated that the weak alkaline urine produced by Fachingen water can actually dissolve concretions of uric acid ; 100 c.c. of a twenty-four hours specimen of a patient's urine were taken on three days, and a uric acid stone was immersed for twenty-four hours in each specimen. The following results were obtained :

Day.	*Urine.*	*Weight of Stone.*		
		Before.	After.	Gain or Loss.
		Gm.	Gm.	Gm.
1	Acid	0·1284	0·1287	+ 0·0003
2	Faintly alkaline with Fachingen water	0·0985	0·754	- 0·0231
3	Amphoteric	0·1852	0·1694	- 0·0158

Klemperer precipitated the uric acid by addition of uric acid crystals and prolonged centrifugalization before using the urine [His and Paul's method (17)]. By this means the uric acid held in solution by the colloidal nature of the urine is separated out, but not that which is combined with alkalis ; it is the only form which is liable in the " uratic diathesis " to be precipitated in the urinary tract. In normal urine Klemperer found that 47 to 88 per cent. of the total uric acid was " free "—that is to say, it could be precipitated by centrifugalization. About 80 per cent. of the free acid can be precipitated, especially if the urine only contains a little urochrome, which has a good deal to do with the colloidal properties of urine. By drinking a bottle of Fachingen daily (4·8 grammes alkaline carbonate per litre) the free uric acid fell to practically nil.

With some reason, therefore, the attempt has been made to diminish the acid reaction in persons subject to calculus formation without going so far as to render the urine alkaline, for there is then the greater risk of calcium deposits occurring, an even worse fate. Hence, in ordering alkalis, or alkaline mineral waters, the individual " urine-reaction curve " of the patient must be carefully studied in order to be able to anticipate an increase or decrease of acidity, and accordingly administer

or withhold the alkalis ; in this way, comparatively small doses of alkali suffice for the avoiding of exacerbations of acidity on the one hand, and absolute alkalinity on the other.

Von Noorden insisted many years ago on the importance of estimating individually the alkalinity of the whole of the urine passed by every patient, a tedious process demanding such scientific accuracy that the advice has been neglected, while hard-and-fast rules have been preferred which save trouble, sound profoundly wise, and cloak ignorance.

Table of Reaction with Various Alkalis and Alkaline Waters.

Mineral Water or Alkali.	*Reaction of Urine varying between—*	*Explanation.*
None	+ 9·5 and − 1·0	The + figure = c.c. decinormal NaOH solution required to neutralize 25 c.c. of acid urine. The − figure = c.c. decinormal HCl required to neutralize the alkalinity.
One tumbler of Wildungen Helene spring every morning before breakfast	+ 8·0 and − 1·5	
Ditto + 3 grammes sodium bicarbonate	+ 6·5 and − 4·0	
The mineral water and alkali in the evening between 6 and 7 o'clock	+ 8·0 and − 3·0	
The mineral water alone in the morning between 11 and 12 o'clock	+ 7·0 and − 1·0	
The mineral water and alkali in the morning between 11 and 1 o'clock	+ 2·5 and − 0·5	

Note.—In the last case the bulk of the urine passed had a weak alkaline reaction, contrary to the previous results.

Salts of sodium (carbonate, citrate, etc.) are generally employed to reduce the acidity, or else waters which contain them (Fachingen, Vichy, Vals, etc.). The salts of the alkaline earths seem to offer certain advantages. Even after very large doses of calcium carbonate have been taken, only traces of calcium are found in the urine, most of it being unabsorbed, or taken up and excreted by the mucosa of the large intestine. With excessive quantities of calcium carbonate (20 to 30 grammes per diem) the urine is scarcely ever alkaline ; in fact, it remains faintly acid. This is a distinct advantage. A still greater benefit is that calcium in the intestinal canal before its absorption, and perhaps also during its re-excretion into the bowel, combines with phosphoric acid, and so prevents its transferrence to the kidneys and urine. Thus the total amount of phosphates in the urine is diminished, and, as the reaction of the urine approaches alkalinity, the proportion of disodium to monosodium phosphates is modified in favour of the former (5). The decrease in phosphates depends in reality on a relative and absolute decrease of the monosodium phosphate, a substance which directly promotes the precipitation of uric acid ; while the relative excess of disodium phosphate, which is capable of dissolving uric acid, is left free to exert a greater effect [Zerner and Ritter (19)].

These experiments, however, only refer to the chemical preparations

of calcium carbonate. Whether the small quantities contained in many waters will act similarly remains to be proved. The short communications of Kish and Heim (20) upon Marienbad and Inselbad waters, which state that no decrease of monosodium phosphate takes place, cannot be regarded as conclusive, for the diet was not kept absolutely constant.

Dilution of the urine, weakening of the acid components, decrease of the relative and absolute amount of disodium phosphate, are naturally not the only factors upon which the solvent properties of urine for uric acid depend ; the presence of various other salts, their proportions, and the amount of urochrome, no doubt all contribute to this end.

A number of conditions have been examined and described by His and Paul (17). It appears that the CO_2 dissolved in the urine has some influence. A considerable part of the CO_2 contained in our food and drink always finds its way into the urine, especially when an endeavour is made to bring about a weak acid or actually alkaline reaction. As an example, the urine (upon a constant diet) contains, when plain water is drunk, 136 c.c. CO_2 per diem, and 480 c.c. CO_2 when an equal amount of the alkaline Fachingen is taken (8).

Excess of CO_2 in the urine favours the precipitation of free uric acid in the urine, but renders it more soluble if combined with an alkali. Despite these many other factors, the reaction of the urine is, after all, the main point in uric acid solution or precipitation, and commands our attention in a special degree, because in the mineral waters we possess an old-fashioned but finely graded means of controlling the individual " acid curve."

In another disease, too, diabetes mellitus, the acidity of the urine concerns us in reference to acidosis. Certainly the reducing of the acidity, or the establishing of an alkaline reaction, is not in this case our actual object ; but it gives us an outward sign that we are providing a sufficient supply of alkali to a system overladen with acid, and aiding the naturally formed ammonia in its task of acid neutralization and acid excretion. Seeing, however, that in mild cases of diabetes from 20 to 40 grammes of $NaHCO_3$, and in severe cases from 80 to 100 grammes, are required to render the urine alkaline, no very striking results can be looked for from the alkaline mineral waters, which at most contain from 5 to 7 grammes of sodium bicarbonate per litre. In the milder and more chronic form of diabetic acidosis these mineral waters are of some value in assisting the acid excretion.

In the rare toxic acidoses of certain fevers much larger doses of alkali are required to alter the reaction of the urine than are necessary in health. In three cases of lobar pneumonia the amount varied between 15 and 25 grammes $NaHCO_3$. Later on, during convalescence, 3 grammes (in six $\frac{1}{2}$-gramme doses) sufficed to make alkaline the whole of the urine passed [von Noorden].

Incidentally, we may mention a case of chronic nephritis, in which a considerable degree of albuminuria became very much less or disappeared altogether so long as the urine was kept alkaline with mineral waters or $NaHCO_3$ (acetic-acid, potassium-ferro-cyanide test). The course of the disease itself was quite uninfluenced. This phenomenon

suggests the need for further investigation. In the few other cases where we have seen this hitherto undescribed relation of albuminuria to the reaction of the urine all the patients suffered first from uric acid renal calculus, and then developed a secondary nephritis (granular kidney).

C.—NITROGENOUS SUBSTANCES.

The effect of various waters on the total nitrogen output is considered in the section Protein Metabolism (p. 901). Here we shall only deal with ammonia and purin bodies.

1. Ammonia.

The excretion of ammonia is not influenced by the non-alkaline mineral waters. It is slightly diminished after the alkaline waters upon a constant diet, although it is not completely suppressed by excessive doses of fixed alkali. The results of Burchard's personal experiments on a constant diet are included in the following table :

Period.	*Mineral Waters and Alkali.*	*Average Values of—*		
		Nitrogen.	NH_3.	Uric Acid.
		Gm.	Gm.	Gm.
7 days	None (fore period)	16·57	0·77	0·686
7 ,,	930 c.c. soda water containing 5·8 grammes sodium bicarbonate daily	16·86	0·67	0·638
7 ,,	930 c.c. soda water containing 5·8 grammes sodium bicarbonate daily	16·04	0·62	0·678
8 ,,	930 c.c. soda water plus 18 grammes sodium bicarbonate and 8 grammes citric acid	13·82	0·26	0·538
8 ,,	930 c.c. soda water plus 27 grammes sodium bicarbonate and 12 grammes citric acid	15·55	0·25	0·517
7 ,,	930 c.c. soda water plus 18 grammes sodium bicarbonate and 8 grammes citric acid	17·29	0·23	0·545
7 ,,	930 c.c. soda water	15·94	0·81	0·603

TABLE SHOWING NH_3 EXCRETION IN CERTAIN DISEASES WHEN MINERAL WATERS WERE TAKEN (VON NOORDEN AND DAPPER).

Disease.	*Fore Period.*		*Alkali Period.*		*In Alkali Period, 700 c.c. of—*	*Per Litre of Mineral Water.*	
	Nitrogen.	Ammonia Nitrogen.	Nitrogen.	Ammonia Nitrogen.		Alkaline Bicarbonate.	Bicarbonate of the Alkaline Earths.
	Gm.	Gm.	Gm.	Gm.		Gm.	Gm.
Obesity (oxaluria)	12·8	0·48	12·6	0·39	Marienbad Rudolf	0·1	1·8
Nephrolithiasis, 1	11·9	0·49	11·1	0·45	Fachingen	3·6	1·2
,, 2	14·8	0·52	15·3	0·46	Fachingen	3·6	1·2
Diabetes (mild) ..	16·2	0·98	16·8	0·71	Vichy Gr. Grille	5·2	0·7
,, (severe), 1	11·3	2·81	13·2	2·90	Vals Madeleine	7·5	1·2
,, (severe), 2	17·8	2·90	18·1	2·85	Vals Madeleine	7·5	1·2

In each case a constant diet was begun a few days before the research, and its accurate administration was confirmed by the constancy of the nitrogen output.

In the first four cases, which were not associated with acidosis, there was a marked, although unequal, decrease of NH_3 output. In all diseases where there is no acidosis this result may be readily obtained, but we must be prepared to find wide variations in individual cases. From a practical point of view, however, there is no object in reducing the NH_3 in non-acidosis cases. Where it really is desirable, as in severe diabetes, the few grammes of alkali which our mineral waters contain are quite ineffectual.

2. Purin Bodies.

Our knowledge of this subject is limited almost entirely to uric acid. The estimation of purin bases under the influence of mineral waters has only been carried out incompletely and in isolated instances.

Long ago it was shown that with a constant diet—a *sine qua non* in all research upon uric acid problems, whose importance has only recently been recognised—the effect of free water-drinking in increasing uric acid is either nothing or very slight and transient [Schöndorff (3)].

Of mineral waters, special interest attaches to the alkaline springs, because from the earliest times they have been recommended with the idea, on the one hand, of rendering uric acid soluble in the urine, or at least retarding its precipitation, and, on the other hand, of abstracting uric acid from the system. It is an undoubted fact that alkaline waters can increase the power of the urine to dissolve uric acid after it has been excreted. Apart, however, from concretions in the urinary tract, the physician is chiefly concerned with controlling the uric acid output in true uric acid gout, a province in which hopes have been raised that mineral waters might prove useful.

In nephritis and leuchæmia an accumulation of uric acid in the blood occurs, but this is regarded as a concomitant symptom, and has never been the special object of treatment.

Uric acid as a "cult" can be read of elsewhere than in a scientific treatise such as this work [Haig (22)]. As we have elsewhere mentioned, the extreme superficiality of the earlier literature of hydrotherapy is made manifest by the fact that either an increase or a decrease of uric acid excretion has been quite indifferently advertised as the priceless boon conferred by some particular water, although there was not the remotest chance of judging which was the more desirable (24).

To-day, since we know that some 50 per cent. of the mother-substances of the purins will reappear in the urine as uric acid and purin bases, and that in gout, with or without uratic deposits, this normal average is, as a rule, not quite attained, we must, in spite of our ignorance of the pathology of gout, regard increased uric acid excretion as a good sign, provided it is not due to increased uric acid formation—a process which may be set up by an increased intake of purin bodies, perhaps by alcohol or even certain drugs ; but inorganic substances, so far as we can ascertain, produce no such result.

(*a*) *Alkaline Waters.*

In healthy subjects alkalis, even in large quantities, produce either no change or frequently a slight decrease in uric acid excretion. Rarely a slight increase may occur.

The following table gives a summary of recorded results obtained with a constant diet extending over long periods :

Observer.	*Uric Acid Output.*	*Uric Acid Output after Alkali.*	*Nature and Amount of Alkali Administered.*
	Gm.	Gm.	
Herrmann (25)	0·762	0·718	5–12 grammes Scignette salts.
	0·666	0·724	10 grammes sodium.
	0·678	0·630	10 grammes sodium lactate.
Laquer (25) ..	0·995	0·969	1 bottle of Fachingen + 15–30 grammes sodium bicarbonate.
Schreiber (16)	0·687	0·759	3·2–6·4 grammes sodium bicarbonate.
Strauss (5) ..	0·838	0·757	3–26 grammes calcium carbonate.
	0·719	0·808	3–30 grammes calcium carbonate.
Salkowski (25)	0·822	0·692	145 grammes sodium acetate in nine days.
Kemptner (25)	0·606	0·605	3·24 grammes sodium carbonate.
	0·606	0·684	8·24 grammes sodium carbonate.
	0·606	0·586	12·24 grammes sodium carbonate.
	0·606	0·435	21·24 grammes sodium carbonate.
	0·606	0·521	12·24–33·24 grammes sodium carbonate.
Hagentorn (25)	0·560	0·605	3·24 grammes sodium carbonate.
	0·560	0·520	16·24–47·24 grammes sodium carbonate.
Burchard (21)	0·686	0·517–0·678	6–24 grammes sodium carbonate (*cf.* Table, p. 948).
Von Noorden	0·505	0·488	7·5 grammes sodium bicarbonate ; purin-free diet.
	0·482	0·456	10 grammes sodium bicarbonate ; purin-free diet.
Gorsky (25) ..	0·712–0·827	0·97–1·06	0·12–0·48 grammes lithium carbonate.
Herxheimer (5)	0·917	0·800	15–21 grammes calcium carbonate.

Why the results vary so much seems inexplicable. The same occurs with the mineral waters, of which we give a table, which does not pretend to be complete, on p. 951, arranged as follows :

First, no definite results.
Second, decrease.
Third, increase of uric acid.

There was never a marked increase of uric acid in any of the experiments. This condition might be expected, for in health no appreciable amount of uric acid is retained in the body. On the other hand, the diminution is in no case so pronounced as with the actual alkali ; but, of course, the amounts taken in the mineral waters are much less.

Although for two centuries and more gout has been treated with alkalis, the experiments which have been made on their effect upon uric acid excretion are all too scanty if the older researches carried out by Heintz's very inadequate method are deducted. The details given are

Observer.	*Uric Acid. Output.*	*Uric Acid with Mineral Water.*	*Nature and Amount of Mineral Water.*	*Alkali per Litre.*	
				Alkaline Bicarbonate.	Bicarbonate of the Alkaline Earths.
	Gm.	Gm.		Gm.	Gm.
Gilardoni (26)	0·473	0·482	2,000 c.c. S. Pelegrino	0·04	0·37
	0·473	0·477	2,000 c.c. alkaline water	5·00	—
Ludwig (27) ..	1·160	1·210	1,500 c.c. Carlsbad Mühlbrunnen	1·28	0·48
Von Noorden	0·800	0·780	1,500 c.c. Carlsbad Mühlbrunnen	1·28	0·48
	0·620	0·590	1,500 c.c. Carlsbad Mühlbrunnen	1·28	0·48
Brandenberg (28)	0·236	0·240	1,000 c.c. artificial Carlsbad Mühlbrunnen	1·28	0·48
Klemperer (8)	0·780	0·720	Fachingen	3·60	1·20
	1·250	0·780	,,	3·60	1·20
Leva (30) ..	0·748	0·689	400 c.c. Tarasper Luciusquelle	4·93	2·30
	0·673	0·636	800–1,000 c.c. Tarasper Luciusquelle	4·93	2·30
Laquer (31) ..	0·612	0·438	500–1,500 c.c. Ems Krähnchen	1·98	0·40
	0·940	0·656	500–1,000 c.c. Ems Krähnchen	1·98	0·40
Determeyer and Büttner (32)	0·975	0·785	300–800 c.c. Salzbrunnen Oberbrunnen	2·20	0·90
	0·875	0·702	500–1,000 c.c. Salzbrunnen Oberbrunnen	2·20	0·90
	1·117	0·921	1,000 c.c. Salzbrunnen Oberbrunnen	2·20	0·90
	0·940	0·903	400–1,000 c.c. Salzbrunnen Oberbrunnen	2·20	0·90
Gilardoni (26)	0·515	0·588	2,000 c.c. S. Pelegrino	0·04	0·37
Schreiber and Zaudy (16)	0·844	0·867	1,300 c.c. Offenbach Friedrichsquelle	2·40	—
	0·844	0·903	1,000 c.c. Fachingen	3·60	1·20
	0·764	0·826	1,300 c.c. Offenbach	2·40	—
Von Noorden	0·500	0·521	1,000 c.c. Marienbad Kreuzbrunnen	2·10	1·30
Brandenberg (28)	0·363	0·394	1,000 c.c. artificial Carlsbad Mühlbrunnen	1·28	0·48

often insufficient—here a slight increase, there a slight decrease, as a result of the alkaline treatment in gout. Haig's (23) experiments are much too short to prove anything. Magnus-Levy (38) was unable to detect any change after the administration of the very alkaline Vichy water. His and Pfeiffer (41) have made numerous estimations, but all without definite results. However, their table is worth quoting, together with a single case of Laquer's, on a constant purin-free diet, and five cases of our own, suffering from typical gout, but observed between the attacks. Four of our patients were on a purin-free diet; the fifth was given in addition 400 grammes uncooked beef. Each figure represents the average of three to six days.

Observer.	Uric Acid Output.			Mineral Water or Drug.
	Fore Period.	Alkali Period.	After Period.	
	Gm.	Gm.	Gm.	
His (39)	0·49	0·43	—	12·0 grammes sodium bicarbonate.
	—	0·46	0·42	
	0·57	0·55	—	
	—	0·41	0·46	
	0·46	0·40	—	
	0·58	0·58	—	Fachingen water 700 c.c.
	0·53	0·59	0·62	
	—	1·01	0·90	
	—	0·26	0·58	0·5 gramme lithium carbonate.
	0·46	0·41	—	
	0·46	0·43	—	
	0·65	0·60	—	
	0·27	0·23	—	
	0·58	0·29	0·46	700 c.c. Salzschlirf Bonifacius.
	—	0·58	0·62	
	0·46	0·41	0·58	1·5 grammes *lysidin.*
	0·43	0·56	—	3 teaspoonfuls *uricedin.*
Pfeiffer (40)	0·73	0·79	—	500–1,000 c.c. Fachingen water.
	0·72	0·78	—	
	0·57	0·59	—	
	0·47	0·59	—	
	0·95	1·09	—	
	0·36	0·77	—	
	0·69	0·93	—	
Laquer ..	0·248	0·207	0·340	700 c.c. Fachingen water + 15 grammes sodium bicarbonate.
Von Noorden and Dapper	0·309	0·366	—	1,000 c.c. Marienbad Kreuzbrunnen.
	0·388	0·329	—	1,000 c.c. Fachingen.
	0·581	0·578	—	
	0·468	0·444	—	1,000 c.c. Vichy Grande Grille.
	0·601	0·588	—	

There is no uniformity about these results; they vary just as much in the healthy as in the diseased subjects, without any apparent reason. It seems as though the effects of alkalis upon uric acid excretion in gout were, if we may judge from a few experiments made with incompletely controlled diet, but small. It will certainly be a great advance when such experiments are conducted on a broader basis, with strict attention to the possible influences of nutrition upon uric acid excretion.

In nephrolithiasis alkalis often seem to increase the uric acid output considerably. It appears from this as if the uric acid precipitated in the urinary tract can really be dissolved by, and excreted in, the "alkalized" urine.

Determeyer and Büttner (32) record one such case:

Uric acid before = 0·512 gramme; with 700 grammes Salzbrunnen Oberbrunnen = 0·611 gramme—a marked increase.

The following table [von Noorden] refers to undoubted cases of nephrolithiasis upon a purin-free diet. The increase can scarcely be regarded as due to any real alteration in metabolism, or to some outpouring of uric acid from the blood, for we have no reason for thinking that in nephrolithiasis there is a retention of uric acid in the blood and tissues.

This complication, when it occurs in gout, has probably quite a different pathogenesis.

Some of the variations are greatly in excess of the table of normal differences (p. 951).

Case.	*Fore Period (4 Days).*	*First Week of Mineral Water Period.*	*Mineral Water.*	*Alkaline Carbonate (Total).*
	Gm.	Gm.		Gm.
1	0·562	0·581	1 litre Fachingen	4·8
2	0·600	0·666	1 ,, Driburg Caspar Heinrich	1·3
3	0·481	0·553	1 ,, Fachingen	4·8
4	0·500	0·511	1 ,, ,,	4·8
5	0·498	0·480	1 ,, ,,	4·8
6	0·568	0·539	1 ,, Vichy Grande Grille	5·9

Practical experience seems to justify the idea that uric acid concretions can be diminished or dissolved by alkaline mineral waters. During such treatment large deposits often disappear from the feet, really owing to disintegration, or decrease in size of the concretion. On the other hand, this does not always happen, and the treatment may prove quite ineffectual. Nor does increased uric acid output invariably result. However, our knowledge is at present so scanty that the question must be left unsettled.

(*b*) *Saline Waters.*

Whether mineral waters, whose chief constituent is sodium chloride, affect uric acid excretion in any way is a question which has not hitherto been the subject of investigations, although for more than a century certain of these springs, such as the Elizabeth spring at Homburg, have had a great name among physicians for the treatment of gout. We have recently made some observations, embodied with a few others in the table on p. 954. (The diet was carefully regulated, and averages of several days are given.)

Although the number of observations is not great, and although they are open to criticism in several directions, yet in all we see a constant difference from the previous tables on alkalis. With a few exceptions the uric acid is increased, sometimes considerably, especially in gouty patients. The case in which the increase was greatest is not included in the above table. The patient, a man aged fifty, was for months never quite free from gouty symptoms ; small swellings came and went without rise of temperature. The diet was always purin free, and included daily 150 grammes beef (weighed raw).

The difference between the second period and the combined average of the four after periods (0·53 gramme) amounted to 0·15 gramme daily, or a total of 1·65 grammes uric acid in the eleven days. As to the process by which the saline waters produce this effect we have no suggestion to

offer. Practical observations alone can give us any information; these results appear so contradictory.

Observer.	*Mineral Water.*	*Uric Acid Output.*			*Disease and Remarks.*
		Fore Period.	"Cure" Period.	After Period.	
		Gm.	Gm.	Gm.	
Dapper and von Noorden (31)	Kissingen Rakoczy	0·470	0·52	—	Chronic alcoholism and gastritis.
	,, ,,	1·400	1·54 (later 1·2)	1·40	Healthy, but persistent excess of uric acid.
	Kissingen Bitter	1·000	1·20	—	Obesity; attack of gout two years later.
Leber (32)	Homburg Elizabeth	1·110	1·29	1·03	Healthy.
	,, ,,	0·940	0·94	—	Healthy.
Von Noorden	,, ,,	0·403	0·44	—	Chronic nephritis with very constant nitrogen excretion (12·1-13·86); purin-free diet.
	,, ,,	0·530	0·49	—	Same case a year later: purin-free diet + 150 grammes meat (weight raw).
Bain & Edgecombe (29)	Kissingen Rakoczy	0·460	0·44	0·54	Healthy.
	Mild Montpellier	0·680	0·66	—	Healthy (NaCl 5·2 grammes per litre).
Von Noorden & Dapper	Homburg Elizabeth	0·300	0·37	0·31	Gout.
	,, ,,	0·570	0·76	0·70	Gout.

The results in uric acid nephrolithiasis are quite different from those in gout. In the former, the saline waters only once produced a very slight increase in uric acid excretion, while in the remainder of the cases there was a slight decrease—the opposite effect to that of the alkaline waters.

Period.	*Nature and Amount of Mineral Water.*	*Uric Acid.*	*Duration in Days (Average).*
		Gm.	
First	800 c.c. Fachingen daily	0·51	6
Second	Ditto + 800 c.c. Homburg Elizabeth	0·68	11
Third	800 c.c. Fachingen only	0·55	6

D.—NON-NITROGENOUS SUBSTANCES.

(*Cf.* also Effect of Alkalis on the Acids of the Acetone Group in the chapter on Diabetes, p. 586.)

1. Glycosuria.

Theoretical considerations of the catalytic effects of alkalis in solution upon the process of oxidation, combined with the actual practical benefits from spa treatment, constantly incline us to attribute to the alkalis and alkaline waters some importance in the treatment of diabetic glycosuria. Külz (33), however, after surveying all the older literature, came to the conclusion that Carlsbad waters did not check glycosuria. Although in individual cases, while drinking Carlsbad, Neuenahr, and Vichy waters, a lessened excretion of sugar has been recorded which can hardly be reckoned as anything but a result of the mineral waters (34), the observers, whose experiments are conducted with attention to external circumstances and constant diet, obtained negative results only.

The later authorities, who took into consideration all the allied conditions, including not only carbohydrates, but also proteins, in their food analysis, are also similarly agreed [Hirschfeld, von Mering, Naunyn, von Noorden (35)]. The sugar excretion, with other factors controlled, behaved precisely the same with or without the mineral waters.

So, too, with large doses of alkali (ordinary $NaHCO_3$ 10 to 40 grammes and more daily). This might be expected from the numerous researches as to the effect of alkalis in diabetic acidosis (36).

Von Noorden, in his clinic, found a very slight and short-lived (one to two days) decrease in glycosuria after taking very large doses of soda, never a large amount or permanent effect.

But no one who is capable of being persuaded by facts doubts the good effect of the " cures " at Carlsbad, Marienbad, Neuenahr, Tarasp, or Vichy, etc. At these resorts many factors contribute with which at present we cannot deal. The discussion belongs more properly to text-books of clinical medicine (35) than to a chapter limited to the effects of mineral waters on metabolism.

We wish to state clearly that we cannot swallow the notion of some mysterious property which is only found in the water at the springs, and somehow escapes from the same water if it is bottled and exported.

2. Oxalic Acid Excretion.

Without entering upon a discussion on oxaluria, a few researches on the effects of mineral waters or their constituents upon the output of this acid is worth a brief mention. The excretion of oxalates was slightly increased by an intake of 2 grammes $MgSO_4$ (from 0·0124 to 0·0176 gramme per diem) [Klemperer (12)]. Kisch (37) obtained the following figures with Marienbad Kreuzbrunnen :

Table (Milligrammes of Oxalic Acid per Litre of Urine).

Before.	*After.*
5·8	1·6
11·7	6·4
11·3	8·9
6·3	9·7

Having at length arrived at the end of this chapter, one can only look back with regret at the superficiality and meagreness of our knowledge of mineral waters and their bearing on metabolism.

Only a few points have been really worked out. In every direction we are faced by the *hiatus valde deflendus*. On the other hand, it must be remembered that much good work has been done, although it has been directed to the indications for practical therapeutics rather than towards the broadening of our knowledge of the complex processes of human metabolism.

LITERATURE.

1. Glax: Balneologie. 1897-1900.

2. Magnus: Ueber Diurese; Vergleich der diuret. Wirk. isotonischer Salzlösungen. E. A. **44.** 396. 1900.—Loewi: Unters. zur Phys. und Path. der Nierenfunktion. Ibid. **48.** 410. 1902. **50.** 326. 1903; **53.** 15, 33. 1905.

3. Schöndorff: Ueber den Einfl. des Wassertrinkens auf die Aussch. der Harnsäure. Diss. Bonn, 1890.

4. Mohr: Ueber das Ausscheidungsvermögen der kranken Niere. Z. M. **51.** 331. 1903.

5. von Noorden: Zur Behandl. der harnsauren Nierenkonkremente. XIV. K. i. M. P. 308. **1896.**—Strauss: Ueber die Einwirk. kohlensauren Kalkes auf den menschl. Stoffwechsel. Z. M. **31.** 492. 1897.—Herxheimer: Ueber die therap. Verwendung des Kalkbrotes. B. k. W. **1897.** Nr. 20.

6. Neuberg u. Albu: Phys. und Path. des Mineralstoffwechsels. 1906.

7. Stadelmann: Einfl. der Alkalien auf den menschl. Stoffwechsel. 1890.

7a. Magnus-Levy: Über Azidosis im Diab. mell. E. A. **45.** 389. 1901.—Gerhardt u. Schlesinger: Ueber Kalk- und Magnesia-aussch. bei Diabetes. Ibid. **42.** 83. 1899.—Stadelmann: Ueber die Ursachen der pathol. Ammoniakaussch. beim Diab. mell. Ibid. **17.** 419. 1883.

8. Klemperer: Beitr. zur Erklärung harnsaurer Niederschläge im Urin. Z. d. p. T. **5.** 48. 1901.

9. Auerbach u. Friedenthal: Ueber die Reaktion des menschl. Harns. Eng. A. **1903.** 397.

10. Rüdel: Einfl. der Diurese auf die Reaktion des Harns. E. A. **30.** 41. 1892.

11. Haussmann: Ueber die Säureausfuhr im Harn. Z. M. **30.** 350. 1896.

12. Klemperer: Behandl. der Nierensteinkrankheit. T. G. **1904.** 337.

13. Quincke: Ueber einige Bedingungen der alkal. Reaktion des Harns. Z. M. **7.** Suppl. 22. 1884.—Görges: Ueber die unter physiol. Beding. eintretende Alkaleszenz des Harns. E. A. **11.** 156. 1887.—Sticker u. Hübner: Wechselbeziehungen zwischen Sekreten und Exkreten. Z. M. **12.** 114. 1887.—Ringstedt: Über die Azidität des Menschenharns. Ma. **1890.** 196.

14. Pfeiffer: Zur Aetiol. und Ther. der harnsauren Steine. 5th K. i. M. **1886.** 444.—Pfeiffer: Harnsäureaussch. und Harnsäurelösung. VII. Ibid. **1888.** 327.

15. Posner u. Goldenberg: Zur Auflösung harnsaurer Konkretionen. Z. M. **13.** 580. 1888.

16. Schreiber u. Zaudy: Zur Wirk. der Offenbacher Kaiser Friedrich-Quelle. Z. d. p. T. **2.** 136. 1898.—Fürst: Ueber die harnsäurelösende Wirk. von Mineralwasserharnen. D. M. Z. **1893.** 203, 213.—Determeyer u. Büttner: Zur Theorie der harnsauren Diathese. D. m. W. **1901.** Nr. 21.

17. His u. Paul: Über das Verhalten der Harnsäure und ihrer Salze in Lösungen. Z. p. C. **31.** 1, 64. 1900.—His: Die harnsauren Ablagerungen des Körpers und die Mittel zu ihrer Lösung. T. G. **1901.** 434.

18. von Noorden: Ueber die Beeinfluss. der Harnreaktion zu therap. Zwecken. Mü. m. W. **1888.** Nr. 39.

19. Zerner: Ueber die chem. Bedingungen für die Bild. von Harnsäuresedimenten. W. k. W. **1893.** Nr. 15.—Ritter: Ueber die Bedingungen für die

Entstehung harnsaurer Konkremente. Mü. m. W. **1895.** Nr. 18. Z. B. **35.** 155. 1897.

20. KISCH: Die Rudolfsquelle in Marienbad. T. M. **1903.** 249.—HEIM: Ueber den Wert und die therap. Wirk. der alkalisch-erdigen Quellen. D. Z. **1903.** Nr. 23.

21. BURCHARD: Ueber den Einfl. des kohlensauren, bezw. zitronensauren Natrons auf den Stoffwech. See STADELMANN, op. cit., Nr. 7. P. 3.

22. HAIG: Uric Acid as a Factor in the Causation of Disease. 1896.

23. Conf. Lit. Nr. 22.

24. DAPPER: Einfl. der Kochsalzquellen auf den Stoffwechsel. Z. M. **30.** 395. 1896.

25. HERRMANN: Ueber die Abhängigkeit der Harnsäureaussch. von Nahrungsund Genussmitteln. D. Ar. M. **43.** 273. 1888.—LAQUER: Ausscheidungsverhält. der Alloxurkörper im Harn. XIV. K. i. M. 330. **1896.**—SALKOWSKI: Ueber die Grösse der Harnausscheidung. Ar. p. A. **117.** 570. 1889.—KEMPTNER, HAGENTORN. See STADELMANN, Lit. Nr. 7.—GORSKY: Ueber den Einfl. des Lithiumkarbonats auf den Stoffwechsel. Ma. **1890.** 346.

26. GILARDONI: Einfl. des alkalis. Mineralwassers auf Stickstoff- und Harnsäureaussch. T. M. **1904.** 69.

27. LUDWIG: Ueber den Einfl. des Karlsbader Wassers auf den Stoffw. C. i. M. **1896.** Nr. 46.

28. BRANDENBURG: Beitr. zur Wirk. von Bestandteilen des Karlsbader Wassers. T. M. **1899.** 633.

29. BAIN AND EDGECOMBE: The Physiolog. Effect of Certain Mineral Waters on the Blood and on the Excretion of Uric Acid. J. P. **1898.** 499. Also "Harrogate Waters, Baths, Climate." London: Longmans, 1906.

30. LEVA: Ueber die Einwirk. des Tarasper Wassers auf den Stoffwechsel. B. k. W. **1894.** Nr. 11.

31. LAQUER: Einfl. der Emser Quellen auf die Harnsäureaussch. B. k. W. **1903.** 586.—DAPPER: N. k. A., H. 5. 1904.—VON NOORDEN: Clin. Treatises on the Diseases of Metab. and Nutrition. Vol. V. 1904.

32. DETERMEYER U. BÜTTNER: Zur Theorie der harnsauren Diathese. D. m. W. **1901.** 336.—LEBER: Zur Phys. und Path. der Harnsäureaussch. B. k. W. **1897.** 956.

33. KÜLZ: Path. und Ther. des Diab. mell. **1.** 31. 1874.

34. SEEGEN: Der Diab. mellitus. 1893.—GLAX: Lehrb. der Balneologie. 1900.—VON NOORDEN: Die Zuckerkrankheit und ihre Behandl. 1901.—LENNÉ: Wesen, Ursache und Behandl. der Zuckerkrankheit. 1898.

35. HIRSCHFELD: Die Zuckerkrankheit. 1902.—VON MERING: Behandl. des Diab. mell., in PENTZOLDT-STINTZING'S Handb. der spez. Therapie. **2.** 1897.—NAUNYN: Diab. mell., in NOTHNAGEL'S Handb. der spez. Path. u. Ther. **7.** 1901.—VON NOORDEN: l. c., 34.

36. See Literature under Diabetes mellitus.

37. KISCH: Ueber den Einfl. der Trinkkur mit alkal. Mineralwässern auf die Oxalsäureaussch. im Harn. T. M. **1896.** 138.

38. MAGNUS-LEVY: Ueber Gicht. Z. M. **36.** 353. 1898.

39. HIS: Die Ausscheid. von Harnsäure im Urin der Gichtkranken. D. Ar. M. **65.** 186. 1900.

40. PFEIFFER: Die Behandl. der Gicht, in PENTZOLDT-STINTZING'S Handb. der spez. Ther. **2.** 37. 1897.

CHAPTER IX

THE INFLUENCE OF BATHS ON METABOLISM

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The action of baths upon the processes of metabolism is a complex question. Every sort of bathing causes an immediate stimulation which is more or less appreciable or intense, according as the surrounding medium differs from that to which we are accustomed. This appreciable stimulus depends on factors which sometimes act in concord, sometimes oppose one another, such as the temperature of the bath and the mechanical or chemical action of the water. The two latter factors are slight except when they are increased by the artificial methods of rubbing, slapping, or adding stimulating substances to the baths like mustard and certain gases. Apart from the appreciable stimulus, baths of various temperatures act directly upon the heat balance by withdrawal of heat, by non-conduction, or by addition of heat. Finally, muscular activity plays a most important part.

These details can, to some extent, be found elsewhere in this book (*cf.* Magnus-Levy, vol. i., p. 244), but their practical importance entitles them to be collected into a chapter by themselves.

Baths may be divided according to their temperature into tepid or "indifferent," and those whose temperature lies above or below the point of indifference, hot and cold baths.

The "indifferent" temperature varies with the individual. Wick (1) places it at 34·8° to 36·4° C., Kisch (2) at 35° to 37° C., Leichtenstern and Riess (4) only at 34° C. According to the latest observer, Oehler (5), the average skin temperature in a room at 20° to 25° C. is 34·1° C.

I.—COLD BATHS.

Warm-blooded animals preserve their intrinsic heat against changes in the surrounding temperature by physical regulation, causing increased or diminished heat loss, and by a change in metabolism which can increase the heat production or chemical regulation.

Physical regulation is under the control of processes in the skin, where, upon exposure to cold, all contractile elements contract and become bloodless, so lessening the loss of heat by radiation, conduction, and

water evaporation. Whenever there is a reasonable prospect of adjusting the temperature of the skin to that of the surrounding medium, this seems to be the mechanism employed, but its action is not lasting; in fact, so soon as a long-continued and severe cold exposure is brought to an end, the anæmia of the skin gives place to a hyperæmia, and warmth is restored.

The primary hyperæmia due to long-continued application of cold is scarcely ever seen in actual practice, though we do see an example of it when the ice-bag is applied for long; on the other hand, the secondary hyperæmia which follows the withdrawal of the cold is well known, and sometimes artificially obtained in practice, being termed in hydrotherapy the "reaction."

Its appearance means increased heat loss, and marks the end of the control by physical regulation. By prematurely breaking off the physical regulation in this manner, the stimulus due to the temperature may be artificially enhanced; the skin reddens prematurely if friction is employed in the bath, or stimulating chemical substances, or CO_2, or other gases are introduced into the water.

In cold baths the stimulus due to a short exposure to cold is probably of but small importance compared with the effect of the "reaction," and perhaps one reason why experiments have not yielded more notable results was that the effect of the reaction was not considered.

Moreover, men respond to changes of temperature very differently from animals, for we can aid physical and chemical regulation by the artificial protection of clothing, which we are wont to adjust in such a fashion that the heat loss corresponds to that which in a naked state would take place at a temperature of 33° C.

The extent to which man is able physically to regulate against cold, when and to what degree chemical regulation and changes in metabolism occur, are vexed questions upon which the most diverse opinions have been expressed. Passing over the old controversies between Liebermeister, Senator, Jürgensen and Winternitz, even in recent times the secondary muscular activity due to shivering has been the subject of keen dispute.

Speck (10), Loewy, and later Johansson, found by the investigation of respiration only, and with methods dealing with short periods, that chemical regulation is always accompanied or called forth by muscular activity. If by a great effort of will the subjects of their experiments were able to avoid shivering and any other movement, then physical regulation alone was manifested.

Loewy says, for instance: "The real mechanism of heat regulation in man consists in an immediate contraction of the skin and its vessels at the first onset of cold, which produces a diminished degree of heat loss capable of fully compensating lack of surrounding warmth to a slight extent only. Beyond this point changes of heat production, a much more deeply-seated process, may be called upon to co-operate; this depends on tonic or clonic contractions of muscle—*i.e.*, tension or shivering which are caused unwittingly or in spite of the will by cold and other stimuli."

Riethus (11) measured with the Zuntz-Geppert apparatus the

respiratory exchange after long periods in baths, which were cooled down from 35° to 27·5° C. in ten minutes, and he found that in healthy men at rest after half an hour in such baths the respiratory gas exchange was maintained at a normal average, and the respiratory quotient was unaltered.

Rubner and Babak (12), obtaining continuous records by their own apparatus, are, however, convinced that in man, as well as in animals, a chemical regulation independent of shivering or other movement must be admitted.

Clinically, this difference of opinion is of no moment; the enforced and unnatural absence of movement is not met with in practice.

Rubner and Babak suggest that an intelligent man, by a supreme effort of will, is capable of repressing, for a time at least, every visible contraction causing muscle waste ("thermic muscle reflex"); the muscle rest so obtained is compared to the effects of curare or division of the spinal cord.

In practice it happens, too, in accordance with this view, that, under natural conditions not involving complete bodily rest, man does actually increase the heat production by exposure to cold, a phenomenon to which many factors contribute.

First, there is the amount of heat loss, and, second, the chemical regulation according to the size of the body and the extent of surface exposed. Rubner has even considered the heat loss as a *function* of the body surface, and has reckoned out a *constant* per square metre of superficies which is applicable to every increase of size and only varies for different animals. This is not, however, universally accepted (*cf.* Vol. I., p. 244). Chemical regulation depends, as Rubner clearly showed in animals, on the state of nutrition and the type of diet, as well as on size. In animals a greater physical heat loss obtains upon diet rich in protein than during starvation. Rubner explains this as a consequence of the "minimal heat requirement," a term which indicates the definite amount of heat loss which under all conditions of the body, and for every temperature, must be covered by heat production. For instance, in a well-fed animal, the margin of normal heat production over the miminal heat requirement is such that, within certain limits, the former is independent of the surrounding temperature, and does not rise and fall with it so long as the minimal heat production suffices for the heat loss at the particular temperature.

In man, apart from the relation of physical regulation to general nutrition, the control of the minimal heat requirement is, within the limits of comfort, very largely a matter of clothing. Between 15° to 26° C. (Rubner) the regulation is exclusively physical. When the temperature is lower than 15° C. an irresistible desire for movement and muscular contraction proves so productive a source of heat that, even though there is an eventual abatement of physical regulation, a considerable increase of heat loss can be compensated; in cold baths this increased heat production always occurs, and is of great importance.

Liebermeister (13) stated: "If in a healthy and moderately fat man we estimate the heat loss which takes place in fifteen to twenty-five

minutes, we find that in a bath of 40° C. the heat loss is about normal; in a bath of 30° C. it is almost doubled; at 25° C. it is trebled; and reaches five times the normal at 20° C."

Liebermeister used the bath itself as a calorimeter, and by simultaneous determination of the body temperature calculated the heat production. By this method the figures are all slightly too high, and his "indifference" temperature was taken to be 40° C.—not the 35° C. mentioned previously; still, it gives a good enough basis to work from, and Rubner's figures calculated from this standpoint are set forth in the following table:

Effect of Bathing on Heat Production [Rubner].

	Temperature of Bath.				
	15° C.	20° C.	25° C.	30° C.	35° C.
Heat production in calories	480	370	240	150	80·0
Heat + 18 calories for heat loss in respiration	498	388	258	168	98·0
Heat – 91 calories, which a man of 60 kilogrammes normally produces	407	297	167	77	7·0
Absolute degree of cooling in the bath ..	81	57	34	12	0·0
Metabolism in bath reduced to grammes of fat	43	31	18	8	0·7
After-effect of bath reduced to grammes of fat	9	6	4	1	0·0
Total effect and after-effect in grammes of fat	52	37	22	9	0·7

Note.—For a bath lasting half or a quarter of an hour the values for heat production, etc., must be halved. The "cooling" figure remains the same if the time is not shorter than a quarter of an hour.

Liebermeister summarizes his observations thus: "The effect of cold water on the body surface of a healthy man under normal conditions during a long-continued application does not lessen the body temperature at all; in many cases it even raises it." So that, within limits, the heat loss may at first be overcompensated.

After a moderately cold bath not lasting too long he showed that there follows a period in which the body temperature is somewhat lower than before the bath; this was called by the older observers the "primary after-effect" (15), so that cooling of the body may occur as the natural result of the "hydriatic reaction"—*i.e.*, of the failure of physical regulation before the active hyperæmia and its increase of heat loss begins. Perhaps the heat loss may be somewhat increased by the evaporation of the water retained on, or in, the superficial layers of the epidermis. Apart from this increased heat loss, Liebermeister, Speck and Winternitz were agreed as to a slight decrease in heat production and a diminution of the muscle metabolism from exhaustion. Speck states that "in this period, when the fall in temperature caused by the bath reaches its limit, the muscular contractions become feebler, and there is a slight decrease in the associated oxidation processes. The fall of temperature ("primary after-effect") now gives place to a fresh process of chemical regulation with increased heat production as its expression

(" after-affect " of the table above); here possibly a slight increase of the body temperature may be established from overcompensation (the " remote secondary after-effect "). The duration and extent of this increased and lowered body temperature varies from a period of many hours to non-existence, according, perhaps, to the different conditions of physical regulation, which sometimes fails early, sometimes late, or to the somewhat inadequate exercise of chemical regulation.

Extraordinary differences may occur, even in the same individual. Jürgensen tells of a man in good health who showed no fall of temperature in or after a bath at 9° C. lasting twenty-five minutes, but four days later in a similar bath under the same conditions his temperature fell to 33·9° C.

These older researches have recently been corroborated and extended by Ignatowski (16) and Rubner; the former worked with an improved water calorimeter and with an anemocalorimeter, and found his results accorded entirely with those of Liebermeister and Lefèvre (17). The lower the temperature of the bath the more vigorously heat production and loss proceed; also, during the first minute in the bath, the organism gives off more heat than in the next, and, finally, in cold baths, after a certain variable period of heat loss, the rate becomes constant. For instance, in a bath of 17·1° C., lasting 2·5 minutes, the heat production was fourteen times the normal: the subject had expended 64·63 calories, and was himself 0·03° C. warmer. It is an interesting point that of these 65 calories, 43·76 were given off in the first minute, and the remainder in the following minute and a half. In another experiment, lasting fifteen minutes, in a bath of 26·75° C., the heat loss in the first five minutes was 43 calories, and 17 calories in the second and third five-minute periods. This agrees with the quarter of an hour bath of Rubner's table. At a temperature of 25° to 26·75° C. about three times the normal heat was produced; for the short bath of 2·5 minutes Ignatowski's figure is naturally much higher.

The decreasing and finally constant rate of heat loss in cold baths may be explained by the fact that the physical regulation (heat loss dependent upon cutaneous blood-supply) is not the only result of appreciable cold, but that there is an actual interference with the heat balance before the contractile elements in the skin can contract completely, or physical regulation reach its maximum. Still, it is more likely that the lessened heat loss in the later stages of the bath is the result of the simple cooling of the skin, whose temperature tends to approach that of the water, so the heat loss becomes purely physical, although the physical regulation will appear to be under some vasomotor nerve control.

At any rate it is known from experiments that the vessels can respond directly to cold. From their work upon heat localization after exposure to heat and cold with subsequent re-heating, Lefèvre, Hirsch and Müller (18) find a marked cooling of the skin results, as may be seen from a couple of experiments of the two latter observers upon rabbits in temperatures of 17° to 18·2° C. (the baths being reduced in an hour from 37° to 17° C.). In warmer baths—*e.g.*, 40° C.—the skin temperature was much higher than that of the liver, muscles, and blood.

Ignatowski has turned his attention to the after-effect also, chiefly with reference to cold baths, which give in the later periods more constant and more pronounced evidences of disturbance of the heat balance. He found that, if no reaction occurred, the heat loss by radiation, conduction, and evaporation continued to decrease even after the bath, while heat production was lessened too. This latter, according to Ignatowski, is directly proportional to the degree of cooling reached, and his subjects were really cooled down by the cold baths. If, on the contrary, a prompt reaction set in, the diminished loss by radiation and conduction could scarcely be observed, and that due to evaporation rose above normal.

Rubner's work (19) dealing with the particular effects of short baths and douches under conditions of real life is of more value than this of Ignatowski, which, after all, only confirms well-known facts.

The following figures were obtained by Rubner with the Zuntz-Geppert apparatus upon subjects standing, sitting, or lying; the time varied from 200 to 300 seconds. The effect of douches was very marked:

	Douche.	*Bath.*
	Temperature 16° C.	Temperature 16° C.
	Per Cent.	Per Cent.
Increase of respired air	54·5	22·9
,, CO_2 output	149·4	64·8
,, O intake	110·1	46·8
Respiratory quotient (varying), representing increased carbohydrate oxidation	0·87–1·02	0·86–1·0

A second case gave the same results.

Rubner is convinced that with short applications there can be no question of an actual interference with the heat balance. He found, moreover, in his first subject, who was accustomed to these baths, that during an hour's rest after the bath there was no noticeable after-effect; his second case, who was not used to them, showed a most noticeable effect on oxygen intake, which was about 32 per cent. after baths between 18° and 28° C. Rubner remarks that in both cases there may really have been a greater after-effect than the figures show, for there is no doubt that baths of this kind affect favourably the energy and fitness for work.

From these experiments it will appear that short cold baths, in which the actual heat deprival is only minimal, cause a fairly marked increase in chemical metabolism, just like the longer ones, where there is greater heat deprival; this is due directly to the movements which the bath sets up. The heat production due to muscular activity exceeds and obscures the katabolism due to the cooling, or in practice renders it quite negligible except under very unnatural conditions. It is impossible to determine the extent of this increased katabolism accurately, because no method can be devised which will deal with muscular activity alone.

Rubner's table suggests a starting-point, but this katabolism is very variable. Whether, besides the influence on general nutrition and the intake of nourishment for the time being, it depends to some extent on the size of the body, and even on familiarity with cold baths, is an open question. Rubner's two subjects show a certain difference in favour of the trained man.

More recent researches referring to the adaptive faculties developed by repeated heat deprival—a factor easily lost sight of in the estimation of katabolism—give different results. Durig and Lode (21) corroborate Nasaroff's observation that dogs subjected repeatedly to cold baths show this adaptive power in that the rectal temperature is only reduced by the first bath, and that subsequent ones cause little or no change before and after. Analyzing Nasaroff's phenomenon, they came to the conclusion that this adaptability was entirely a matter of physical regulation, and did not involve any alteration of metabolism. They advance the hypothesis that the vasomotor reaction is not controlled in these repeated baths by the action of the involuntary muscle of the bloodvessels, but by a loss of susceptibility to the temperature stimulus of the cold—a view which assorts ill with all the talk in "hydriatic" literature about exercise of the capillary musculature making the reaction appear more readily.

With reference to the increased metabolism proved to be due to cold baths the question arises, What is the chief constituent of the body that is used up in the process? All observers agree that only non-nitrogenous material is oxidized. Voit, in his masterly researches, showed that, so long as cold produces no decrease of the intrinsic heat, there is no increase of protein metabolism—*i.e.*, the increased heat production is attributable solely to muscular activity. Rubner's increased respiratory quotient bespeaks the same conclusion.

If, on the other hand, material disturbance of the heat balance occurs, such as may be produced by very energetic bath processes, the protein metabolism does appear to be affected.

Warm-blooded animals, as Sander, Ezn (23), and Voit (24) showed, behave when the body temperature falls just like cold-blooded—that is to say, their metabolism as a whole diminishes. The protein disintegration under these conditions, however, rises above the normal, as Lépine and Floward (25) and Dommer (26) demonstrated in animals, and Formanék (27) in men, whose temperatures he reduced to 32° C.

Apart from this increased metabolism of protein due to excessively low temperatures, very little is known of the nitrogen balance after cold baths. In particular, there is a want of accurate work with recent methods on the relations of its individual components. Strasser's results (28) are not of very great value. He estimated the NH_3, urea, and extractives after repeated baths.

The only reliable investigations are those of Schilling (29), who, after cold baths, showed a marked increase in the ammonia excreted in the urine, which was not associated with a simultaneous increase of total nitrogen. He regarded this as due to acidosis.

II.—HOT BATHS.

There is no mechanism corresponding to the increased oxidation by which lack of heat is compensated whereby the organism can reduce its heat production or decrease its metabolism when exposed to heat or when heat loss is prevented. Only a very trifling diminution is compatible with the maintenance of existence. The "increase-mechanism" of the working organs can alone be controlled; the "minimal metabolism" cannot be lowered.

In small animals, like dogs, the heat production is independent of chemical regulation in a surrounding temperature of 30° C., and can be no further reduced. In man the temperature is, perhaps, a little higher (*cf.* table, Vol. I., p. 246).

Exposure to heat probably only affects the body temperature by physical regulation, which in normal men is chiefly a question of evaporation. If, when its limits are reached, this physical regulation proves insufficient, the body temperature rises unchecked.

It may be taken as certain that a rise of temperature means an increase of metabolism. Long ago Pflüger (30) was able to show that the heat production in suckling animals exposed to heat was increased—for instance, in rabbits it rose by 6 per cent. if the body temperature was raised 1° C. The contradictory observations of Litten (31), Simanowski (32), and Speck (33), may be explained by the fact that, during the heating for short periods only, the effects upon metabolism may become equalized during the succeeding hours, and therefore in the twenty-one hour experiments such as Simanowski carried out may not come into evidence at all. Even Voit (34) has at last accepted Pflüger's opinion.

More recent work has shown that this holds good for man (35-37, 39). Winternitz's (35) results are especially important, because they show that the increased consumption of oxygen caused by a moderately hot bath far exceeds that due to fever, which, as is well known, only averages about 20 per cent. He found this increased consumption even with quite gradual and moderate heating, which did not cause any mechanical change in the respiration. The facts are detailed in the table on p. 966, and there seems every reason for accepting them.

The experiments of Winternitz, which were subsequently repeated with the same results, show a marked increase of metabolism with hot baths, thus confirming the respiratory analyses of Linser and Schmid, who determined the gas exchange of a man suffering from ichthyosis, and found the oxygen consumption increased in a very hot room by 100 per cent. Salomon, on the contrary, observed that hot air and light baths in healthy persons affected the metabolism very much less, in spite of the processes being very powerful, and lasting some four hours. The increase of the oxygen consumption, after deducting the amount attributable to increased work done, amounted on an average to only 15·9 per cent. Salomon justly draws attention to the extraordinarily

Date.	Respiration per Minute.	Oxygen Requirements per Minute.	CO_2 Production per Minute.	Respiratory Quotient.	Increase Respiration per Minute.	Increase Oxygen Requirements per Minute.		Increase CO_2 Production per Minute.		Remarks.
						In c.c.	Per Cent.	In c.c.	Per Cent.	
—	c.c. 4,067	c.c. 176·8	c.c. 138·5	0·78	c.c. —	—	—	—	—	Average normal value.
August 11 ..	7,814	322·9	243·0	0·73	3,726	159·2	91	114·2	88	After 47 minutes in hot bath.
,, 13 ..	9,086	318·0	272·5	0·85	4,852	143·8	82	133·3	95	,, 23 ,, ,, ,,
,, 18 ..	10,301	363·6	316·2	0·86	6,085	190·7	110	182·4	136	,, 35 ,, ,, ,,
November 25 ..	6,052	248·7	214·2	0·86	2,068	71·1	39	78·0	57	,, 23 ,, ,, ,,
	7,021	292·0	251·3	0·86	3,037	114·4	64	115·1	84	,, 48 ,, ,, ,,
,, 29 ..	6,049	283·0	231·6	0·81	2,129	115·2	68	96·8	71	,, 20 ,, ,, ,,
	8,431	321·2	282·4	0·87	4,511	153·4	91	147·6	109	,, 45 ,, ,, ,,
August 11 ..	4,410	204·4	151·4	0·74	322	30·7	17	22·6	17	48 minutes after the bath.
,, 13 ..	4,358	182·9	151·1	0·82	120	8·7	5	11·9	8	45 ,, ,, ,,
,, 18 ..	4,812	207·9	156·7	0·75	718	35·0	20	22·9	17	45 ,, ,, ,,
	3,814	193·3	143·8	0·74	350	20·4	11	10·0	7	75 ,, ,, ,,
November 22 ..	4,165	202·0	143·3	0·71	Decreased. —	35·6	21	13·5	10	45 ,, ,, ,,
,, 25 ..	4,314	225·2	168·2	0·74	330	47·6	26	32·0	23	30 ,, ,, ,,
,, 29 ..	4,550	197·9	149·2	0·75	630	30·1	17	14·4	10	45 ,, ,, ,,
	4,209	215·5	164·1	0·76	289	47·7	28	29·3	21	78 ,, ,, ,,

small effect on the gaseous exchange compared with that on the body-heat, body-weight, and general well-being, which is so pronounced. In his experiments an overheating was actually produced which not only equalled, but surpassed, that obtained by Winternitz, so one can scarcely assume the existence of a better physical regulation in the hot-air bath as being responsible for the difference.

Perhaps the chemical action of hot water on the skin, to which Bier (40) refers confidently, may affect the issue. The influence of this upon metabolism will be discussed later. But it does not help to explain the disagreement between Salomon's results and those of Linser and Schmid, who worked exclusively with the hot-air bath. Probably the absence of sweating causes the subject of ichthyosis to behave somewhat differently from a normal person. In Winternitz's table it will be seen that the CO_2 output and oxygen intake go hand in hand, while the respiratory quotient shows only trifling variations in the direction of increase.

Linser and Schmid, on the other hand, found the oxygen consumption increased as much as 100 per cent., the CO_2 output less so (40 per cent.), while the respiratory quotient fell to 0·429. They remark upon this difference, with a reference to the investigations of Riethus and Loewy, who in febrile conditions noted a constant fall in the respiratory quotient (*cf.* Vol. I., p. 199). Riethus insists emphatically that this fall does not depend on the increase of temperature *per se*, but on the toxæmia.

Moreover, the facts are not so utterly at variance as at first sight appears, for Winternitz in his second research and Salomon also found the respiratory quotient diminished, although not to the same extent as did Linser and Schmid. This may be due to the fact that its variations depend on other causes than the mere heating, for the respiratory quotient bears no constant relation to the temperature.

From a teleological point of view, increase of metabolism and heat production seem quite inappropriate consequences of overheating, and they cannot be explained simply on the ground of increased work by the heart, or of respiration, or of sweat secretion. Winternitz calculates that of the 40 to 111 per cent. increase of oxygen intake and CO_2 output, according to the duration and heat of the bath, after subtracting the proportion due to increased work, there still remains 30 to 75 per cent. unaccounted for. Here Pflüger's theory may be applied that as soon as the heat balance is impaired in warm-blooded animals, the oxidation processes obey the law that otherwise holds good for organic and inorganic bodies. Oxidation increases with a rise in temperature and decreases with a fall.

Comparatively few investigations have been made into the after-effects of hot baths.

The results of the earlier observers, Jürgensen, Baelz (42), and Speck, show that the body temperature can still go on rising for a short time after the end of a hot or vapour bath. Speck offers the following explanation : " The thoroughly heated skin must for a while continue to act as though it were still in the hot bath." This is not so improbable when we remember that the skin temperature in a hot bath is much higher than that of the blood, muscles and liver [Hirsch and Müller (43)].

Baelz, moreover, stated that he had not observed a subsequent abnormal fall of temperature by way of compensation. Wick, who has completely followed out the course of the temperature after hot baths, concludes that after about two hours the normal is regained, and says that here and there he even observed slightly subnormal temperatures. Ignatowski corroborates this : he met with a fresh secondary rise after the subnormal temperature. It seems a striking point that all authorities are agreed that at any rate no considerable fall of temperature occurs after hot baths, although the skin is very vascular for some time, and the heat loss must be greatly increased. Ignatowski found the loss by conduction and radiation, and especially evaporation, increased after hot baths, the latter twice or three times the normal ; yet the body temperature only falls very slowly, owing, probably, to the fact that even after the bath the increase of heat production continues. Both Ignatowski's calorimetric estimations and Winternitz's analyses of respiration prove this. Winternitz found, for instance, the oxygen consumption in one case increased by 29 per cent. even seventy-five minutes after the bath, at a time when the breathing showed practically no change (*vide* Table).

In a few cases Ignatowski failed to observe any increase of heat production. He states expressly that in this event the subjects of the experiment showed signs of great fatigue. There may be a good deal in this suggestion. Salomon was not able to demonstrate any after-effect on metabolism in his experiments with hot air and light baths.

Rubner investigated the effects of short-lasting hot baths. It appears that even in these, where the heat balance can hardly be disturbed, the volume of respired air, CO_2 output and oxygen intake were increased, but to a far less degree than in the case of cold baths. The following table gives a comparison of results in a hot and a cold bath :

	Hot Bath.	*Cold Bath.*
	Temperature 44° C.	Temperature 16° C.
	Per Cent.	Per Cent.
Increase of inspired air	18·0	22·9
Increase of CO_2	32·1	64·8
Increase of O	17·3	46·8

It is remarkable that the respiratory quotient showed the same increase, in both instances rising from 0·86 to 1·0, from which it seems not improbable that exposure to considerable heat may lead to a demand upon the organs for increased work, just as with cold baths. There is, however, another possible explanation, the chemical action of hot water referred to before. Rubner has done some work on the after-effects of short hot baths and douches, and demonstrated an hour afterwards a decrease both in the volume of respired air and in metabolism ; this was especially marked when the experiment was made with the subject

of experiment in the standing position: the oxygen intake then fell by 26·7 per cent. There is a considerable difference in the after-effects of hot baths according to their length of duration. It is uncertain what causes the decreased heat production described by Rubner as occurring after short hot baths; the sense of fatigue produced and the consequent muscle rest must be taken into consideration.

Since hot baths increase the rate of metabolism, the same problem presents itself as in cold baths, What materials are consumed in the process? In cold baths it is certain that the metabolism of proteins does not account for it, but in hot baths the case is different, provided that the heat is sufficiently great to raise the body temperature considerably, and not allow it to be maintained constant as in cold baths. This increase of protein metabolism has been demonstrated not only in animals (44 to 47), but also in man (48, 49). Formanék thinks that in man a single hot bath has not so marked an effect as repeated baths on several days. Bornstein (50) failed to find the increased protein metabolism, but it may very well happen that there was a deficient excretion of its products in the urine, or, as Winternitz pointed out, a considerable nitrogen output might pass unnoticed in the sweat. Negative results cannot shake positive results obtained with accurate methods. All this earlier work assumes, and great stress was laid upon the fact, that intrinsic overheating was actually and readily obtained. We shall see presently that more recent and complete experiments, which did not start off with this assumption, showed no sign of increased protein metabolism. The view has been advanced by Voit that increase of protein metabolism is not a primary result of increased body-heat. First of all the output of non-nitrogenous material is increased, and, when this "protein-saving" device is exhausted, the protein balance becomes as a secondary result exposed to attack. Voit supports his view by two examples. He found, as did Schulte Overberg previously (51), a very small amount of glycogen in the liver after artificial overheating; then by giving 30 to 40 grammes of sugar he found he was able to prevent (*vorzubeugen*, he expresses it, without actual figures) the increased nitrogen excretion. Voit's methods are so unassailable that it seems very remarkable that cold, in contrast to heat, does not cause any increase of protein metabolism as long as the body-heat does not fall, although the general rate of metabolism is so greatly raised, and "a primary consumption of non-nitrogenous material" is proved to exist.

But the analogy between cold and heat is very close. If the heat balance is violently disturbed, and the constant temperature of the body can no longer be maintained, then in both cases the protein balance is upset.

Whether the increase of protein metabolism due to mechanical overheating is the same process as occurs in fever is more questionable. Martin (53), in some researches made at my suggestion, found the *albumoses*, which are almost constantly present in fever, always absent in overheating, a fact corroborated by Linser and Schmid. I admit that exception has been taken to the methods employed.

Yet even if Martin's results are not absolutely reliable, they are to

some extent supported by the accurate and important researches of Linser and Schmid on protein metabolism in fever and overheating.

Linser and Schmid made further experiments in cases of ichthyosis; these patients have the peculiarity of not sweating, and can be overheated with comparative ease, since their powers of evaporation are very limited. Merely remaining at rest in a room heated to 30° to 38° C. is enough to raise their temperature to 38° or 39° C. for a whole day. In other subjects physical regulation proved to be more or less adequate; they must, as a rule, be kept in a hot-air bath to raise their temperature.

Linser and Schmid conclude that external heat, even applied for many days, does not cause an increased protein metabolism, provided the body temperature does not exceed the limit of 39° C. As a rule, when 40° C. is reached, the *nitrogen output* is increased. If the process of heating is abrupt, this increase very readily occurs. Linser and Schmid also maintain that in febrile diseases with high temperatures the hyperthermia as such has no effect on the nitrogen output, which is simply due to the toxæmia; they proved that administration of carbohydrates limits the nitrogen output in fever, though not to the same extent as when the body temperature was normal, a fact which has an important bearing on Voit's theory; but they do not agree with him in thinking that the increased nitrogen output in conditions of hyperthermia is simply a question of lack of oxidisable non-nitrogenous material.

Moreover, Senator and Richter (52) quite recently have denied any definite relation between the amount of glycogen in the organs and the rise of temperature; they even suggest that the increased nitrogen output is not nearly so often met with as the increased heat production. According to a calculation made by Winternitz, increased protein disintegration is associated with increased heat production in only about one-third of the observed cases, so that it is reasonable to conclude that under the influence of overheating an increased consumption of non-nitrogenous material actually takes place. Lastly, as bearing upon this question of the constituents which contribute to the increased nitrogen output, Driver (55) demonstrated that the marked increase of *purin bodies* in the urine described by Frey and Heiligenthal (54) could not be found. A slight increase, amounting to about a decigramme, was indeed found both by us and by Linser and Schmid.

The excretion of *ammonia* was shown by Linser and Schmid and Schilling to run parallel with that of total nitrogen, but it was noticed that the increase of ammonia was always a little less than that of total nitrogen. These authors found the same to hold good of the *amino-acids*. The *phosphoric acid* curve was, however, always parallel with that of the nitrogen.

Lüthje (56) has made an extremely interesting observation on the influence of temperature on pathological conditions of metabolism. In a dog with pancreatic diabetes, high temperatures caused a slight, low temperatures a marked, increase of sugar excreted. Lüthje claims to have seen a striking and rapid alteration in the limits of tolerance in men when they are allowed to stay for a long time in a temperature of 30° C. Bendix (57) succeeded in producing glycosuria in man by the

administration of large amounts of grape-sugar simultaneously with diuretics; this glycosuria was suppressed by free sweating, and the sugar appeared in the sweat.

III.—TEPID OR INDIFFERENT BATHS.

We have already mentioned that the limits of indifference vary in individuals. Exactly indifferent temperatures have no effect on metabolism, whatever the duration of the baths. All observers, both early and recent, are agreed on this point, which is borne out by the possibility of remaining a week or so in a constant water-bath without injury, providing the " indifference " is accurately adjusted to the metabolism.

IV.—MECHANICAL OR CHEMICAL STIMULATION.

In the first place it must be recognised that such stimulation has the effect of breaking down physical regulation prematurely, and so unduly increasing the heat production. Winternitz (58) demonstrated this by showing that friction applied in a cold bath caused an earlier fall in the temperature than a bath without the friction. Winternitz and Pospischil (59) found by respiratory analysis that this rubbing whilst in a cold bath increased the oxygen intake and the CO_2 output more than the bath alone. Still, it cannot be taken for granted that the breaking down of physical regulation is the sole result of mechanical stimulation; it may directly promote metabolism. At least, Winternitz fell back on this explanation for the very marked increase of heat production which he observed in a hot-sand bath, which was far beyond Salomon's records in the hot-air bath: he suggests that both the nature of sand and the pressure of its weight produces a considerable stimulation of the skin. And this view is the less likely to be dismissed, since Winternitz was able to prove that chemical stimulation can increase metabolism.

Paalzow (60) showed that by brushing the skin, or by the application of mustard paste, an increased temperature can be obtained in man, and by the use of mustard paste in rabbits an increased heat production may be demonstrated by respiratory analysis. Both the oxygen intake and the CO_2 output were raised, the first from 6·7 per cent. to 51·2 per cent. Winternitz, using a reliable method, found that mustard in a therapeutically active form added to an indifferent bath served to increase the oxygen intake and CO_2 output by about 25 per cent. without affecting the respiratory quotient. The increase is proportional to the length and strength of the bath, which, as Winternitz showed, has nothing to do with the act of respiration or the visible muscular contraction, but simply with an increased tissue metabolism; and, since Köstlin has proved that protein metabolism is unaffected, it must be assumed that Winternitz's increased heat production is provided by oxidation

of non-nitrogenous material. Yet it is rather remarkable that the respiratory quotient shows no variation indicative of increased carbohydrate oxidation.

Of greater clinical interest than the action of mustard baths is that of brine baths.

The earlier researches of Jacob (61 to 63) and Leichtenstern showed that there was no difference in the action of plain water and concentrated brine baths. In 1871 Röhrig and Zuntz (64) showed that the oxygen intake and the CO_2 output in rabbits was considerably greater than in plain water at the same temperature. Winternitz found that baths containing common salt, Stassfurt salts, or pure potassium chloride, produced but little change in the metabolism of healthy adults (the highest figure was 15 per cent. after a bath lasting an hour).

The protein metabolism after *brine baths* has been frequently investigated. Dommer obtained in a dog a marked rise in the nitrogen output in an indifferent bath (brine = 4 per cent.), but later observers, except Robin (66), have not corroborated this. Keller (67) and Köstlin (65) actually described a decrease. Robin and Keller's methods are not beyond criticism, but Köstlin's results, obtained in Von Mering's laboratory, must be accepted without hesitation. Köstlin found that common salt baths have no effect on the protein balance, but that Stassfurt salts cause a slight decrease. This he considers to be due to the presence of potassium chloride, for he found the same decrease in baths containing pure potassium chloride; while the chlorides of magnesium and sodium, which are also present in Stassfurt salts, failed to produce a similar result.

The majority of the investigations tend to show that the effect which is experimentally demonstrable is very trifling, and yet clinical experience tells a different story. Every physician is acquainted with the marked effect of brine baths upon strumous children; in fact, a very close watch has to be kept on the patient's weight. In this connection Heubner's work (68) is most important, for his researches were made not on healthy adults, but on strumous children of both the "phlegmatic" and the "sanguine" type.

True, no respiratory analyses were taken, but apart from this the experiments show that on children of this sort brine baths act definitely. The body-weight was found not to increase, in spite of liberal feeding; the nitrogen output was increased, and the storing up of protein was correspondingly lessened; no chloride retention could be demonstrated. Heubner, who was particularly observing the effect of brine baths on circulation, came to the conclusion that metabolism is affected in two ways—"by the production of an ebb and flow of blood between the viscera and the integument, and by some action on the terminations of the peripheral vasomotor, and perhaps even on the endings of the sensory nerves."

Loewy and Müller (70) give some data as to respiratory analysis in their work on sea air and *sea baths*. The only previous investigations had been those of Bennecke (71) in 1858, which showed an increase of urea in the urine and a decrease of uric acid and phosphates. Loewy

and Müller analyzed the respiration in three cases from three-quarters to four and three-quarter hours after the baths (taken like ordinary cold sea baths). They did not omit to determine the effect of a cold bath as such, and also of the salt contained in it; and also, in the last case, they had to consider the effect of an indifferent warm sea bath. They were particularly anxious to ascertain whether a longer after-effect was produced by sea baths, and the method adopted was similar to that of Rubner's, of whose publication they were unaware.

Firstly, they observed most marked individual changes in the type of respiration approaching the Cheyne-Stokes breathing, and the chemical relations were altered, for the mechanism and chemistry of respiration are very closely associated.

In all three cases the gas exchange showed an increase, the least in one who proved quite indifferent to sea air, the most in a subject in whom the mere effect of the climate had caused the resting metabolism to reach the highest level. It seemed, also, that the effect of sea baths was not limited to the actual time of their duration, and it is very interesting to note that the effect on the appetite shows no relation to the metabolism. These experiments are, therefore, the more valuable because they were carried out under the ordinary conditions which obtain with sea-bathing. The individual variations agree pretty well with Rubner's determinations (p. 966).

Several authors describe a fine deposit of salt crystals remaining on the skin after brine baths. Hiller (69) thinks this may stimulate the skin no less vigorously than the bath itself. Schwenkenbecher (73), who has recently made resorption by the skin his special study, suggests that the water taken up by the deposit of a hygroscopic salt constitutes a stimulus. Stimulation of the skin increases oxidation, and with reference to this, Frankenhäuser (72) has made the odd suggestion that in man, when the aqueous tension of the respired air remains constant, the excretion of water depends primarily on the moisture of the skin, and when, after a brine bath, this fine layer of salt is deposited, it must form, with the moisture of the skin, a concentrated salt solution. Salt solutions, however, evaporate more slowly than plain water, so this deposit lessens the heat loss, and has really the effect of a cloak. The hygroscopic property of the salt is, then, more important than the actual amount crystallized out on the skin. Frankenhäuser showed experimentally that a spot of skin impregnated with a hygroscopic salt solution does actually give off less heat than the plain skin under like conditions. Heubner has estimated quantitatively this alleged deposit in his cases after the bath; it turns out to be an amount barely recognisable.

Winternitz has worked out the action of CO_2 baths on metabolism. The results showed a remarkable increase in CO_2 output without a corresponding increase in the oxygen intake. The total volume of respired air was greatly increased. Winternitz explained the increased CO_2 output by a resorption of CO_2 by the skin, stating that the increased respiratory volume was accounted for in part by the increased CO_2 resorption, and in part by the appreciable stimulation of the skin which the CO_2 produces. The addition of NaCl and $CaCl_2$, which are present

in the natural springs, increased the resorption of CO_2. Zülzer (74), with oxygen baths, which have lately been recommended as substitutes for the CO_2 baths, found a very trifling resorption of oxygen—about one-hundredth of the total inspired amount. It should, however, be noted that probably Winternitz's experiments, valuable as they are, have no bearing on the practical problem, since he worked entirely with indifferent warm baths. The effect of CO_2 baths in practice amounts to this—that the CO_2 makes a cold bath endurable for a longer time, because the skin is reddened, and the cold is not so readily felt. Actually, the effect of a cold plain bath, and that of a CO_2 bath at the same temperature, appear from the respiratory analyses to be precisely the same. It will naturally be supposed that the heat loss and secondary heat production will be increased by a CO_2 bath where the physical regulation is prematurely broken down and the skin reddened as if by friction. From an analysis made by Senator, it is open to question whether a cold CO_2 bath causes even as much heat loss as a plain water bath.

In baths which contain CO_2 the skin becomes covered with bubbles of gas. Senator and Frankenhäuser (75) have shown that there is a considerable difference in heat conduction and heat capacity between CO_2 and water. Carbon dioxide at 25° C. acts as a " warm " stimulus, water at 25° C. as a cold one ; it is to this that the authors attribute the specific effect of these baths. We may readily conceive that the parts of skin covered with CO_2 give off less heat than those touched by the water, and in theory the CO_2 bath might cause a less heat loss than plain water at the same temperature. This is only hypothesis, for no work has been published on the subject. From the practical standpoint, I can assert with certainty that the temperature in fever can be as successfully reduced with cold CO_2 baths as with plain cold water.

Sulphur baths have no effect on metabolism [Winternitz (59), Bain and Edgecombe and Frankling (114)].

Peat and mud baths cause the same deposit on the skin as CO_2 baths. The smaller heat capacity of the peat compared to water allows a higher temperature to be maintained. Metabolism may also be affected by the chemical action of peat (free acids are always present), by its consistency, and by the manner in which it prevents movement. No respiratory analyses are available. The conclusion at which Nenadovicz (76) arrives—that cold peat baths " exhaust the muscle substance, but favour the nerve substance, while hot peat baths have the reverse effect " —appears to be a hasty generalization not based on very satisfactory data.

Of late there has been a great talk about *radio-active substances*, or radium emanations, in baths. Assuming them to be present, all that can be said is that no one can contradict their supposed effect on metabolism of the tissues ; but there is no positive evidence which is anything better than guess-work.

Siegel's (77) researches deserve mention here, for they show the influence of baths in general on the *oxidation of benzol* in the system. Siegel investigated " series " of days, on some of which baths were administered and some not. The individual variations were considerable,

but, at any rate, cold baths certainly increased the phenol excretion, and sweating processes had a more marked effect.

Brine baths at indifferent temperatures gave no result. Hot brine baths of various temperatures were much more potent and lasting in their effect than plain water of the same temperature.

To sum up, it will be seen that both hot and cold baths increase the processes of metabolism, but tepid baths have no such effect; that the addition of mechanical and chemical stimulation increases their effect, either through breaking down the physical regulation or through some specific action. The increase of metabolism thus obtained is most difficult to estimate; even the determination of the after-effect cannot pretend to give us an adequate idea, because the effect of movement cannot be expressed in terms. In general, cold baths have the greater effect, because they lead to more movement. With hot baths, which cause a greater sense of fatigue and less movement, the same argument does not apply. If we suppose, for instance, that a hot bath lasting an hour were to increase the rate of metabolism by 100 per cent., it would only affect one twenty-fourth of the daily quantity of calories. Clinical experience suggests that sweat cures for obesity depend far more upon impairment of the appetite than on any change in metabolism. My own idea is that these secondary effects, which are generally acknowledged to result from continual cold baths, are the important part.

Qualitative decrease of metabolism (increased protein disintegration) does not come practically into the question, for these extraordinary methods, which interfere with the body heat, are not applied therapeutically. The importance of individual variations cannot be too strongly emphasized.

The question of the respiratory mechanism is purposely not very seriously considered, for it only bears on metabolism inasmuch as it produces increased muscular action.

V.—EFFECT OF BATHS ON THE SECRETIONS.

Cold baths increase *the flow of urine* temporarily, but with a healthy circulation these variations are so compensated that the total amount for the twenty-four hours remains constant. The increased secretion depends upon the raised blood-pressure due to the cold, perhaps also on vasomotor changes in the calibre of the renal vessels (78 to 82).

With defective circulation cold baths may, by diuresis, tend to improve the state of the circulation.

Hot baths, of course, since they promote sweating, diminish the renal excretion, and the amount of sweat may be very considerable—as much as 1 kilogramme and more.

No very exhaustive research on the balance of mineral substances has been made beyond that of Linser and Schmid on phosphates (39).

Strasser and Kuthy (83) and Krauss (84) have determined the *acidity*

of the urine after hot and cold baths. In spite of using the same method (Lieblein's modification of Freund's), these observers came to utterly contradictory conclusions. Krauss found that hot baths caused a decrease, and cold baths an increase, of acidity; Schilling, as we stated before, found a marked increase of ammonia after cold baths without simultaneous increase of total nitrogen elimination; so Krauss's result should be regarded as more reliable than the contrary observation of Strasser and Kuthy. The increase of *ammonia* described after hot baths by Schilling and Linser and Schmid is proportional to the total nitrogen.

In animals after exposure to severe cold von Araki (85) noted almost constantly the appearance of *albumin*, *sugar*, and *lactic acid* in the urine. He explains this as the result of incomplete oxidation, regarding these bodies as intermediate products of metabolism.

Sugar and lactic acid only occur with rapid and excessive cooling, and are not met with in actual practice.

Albumin is commonly met with after cold baths as an occasional occurrence in certain persons predisposed to it—for instance, in the cyclical albuminuria of adolescence [Rem Picci (86)].

Paroxysmal hæmoglobinuria is well known to occur after cold and cold baths. Naturally, perhaps, certain hæmolysins are blamed for the condition. Donath (87) gives a full survey of the subject, and from his own researches and those of others he considers that hæmolysis is neither to be regarded as the direct result of cold on the erythrocytes, nor as some mechanical injury to them, but that it is much more likely to depend on some hæmolytic property imparted to the plasma by cold.

Several French authorities have described Bouchard's *urotoxic quotient* as greatly raised after cold baths in acute infections [Roque and Weil (88), Igelranz and Déhon (89)].

The secretion of sweat is of much more moment than that of the urine secretion, for it forms the first line of defence in physical regulation against heat. The amount excreted may be very large if not checked artificially, and the output can be so easily balanced by increased intake that even after the long-continued application of "sweating processes" the body-weight does not fall.

The excretion of organic substances and salts in the sweat has been repeatedly investigated. Varying quantities of salts, especially chlorides, are excreted. Camerer (90), the latest observer, found in 100 grammes of dried substance: ash, 50·60 grammes; fat, 10 grammes; nitrogen, 10 grammes; and of the nitrogen 34 per cent. was urea nitrogen and 7·5 per cent. NH_3 nitrogen.

Magnus-Levy found a little uric acid in the sweat of healthy persons; this was absent from that of gouty subjects.

The freezing-point of the sweat Strauss found, as a rule, below $-0{\cdot}39°$ less than that of blood-serum.

In kidney disease both nitrogenous and inorganic bodies seem capable of being excreted in the sweat in increased quantities. Leube was able to demonstrate urea in crystals on the skin. More recently, von Noorden (91) and Köhler (92) estimated the nitrogen in the sweat of kidney

diseases, and the latter found fairly considerable nitrogen values. Strauss (93, 94) found the freezing-point much more often lowered in these cases than in health, and especially so in the chloride-free portion. Arguing directly from this, he recommended the use of "sweat processes," with free water-drinking, as a remedy for uræmia. He advanced a hypothesis concerning the importance of chloride retention in the production of œdema, stating that for renal dropsy sweating should only be allowed provided the sweat contains at least 0·6 per cent. of NaCl.

Bendix (95) made some interesting observations on the freezing-point of the blood. He could neither alter it in healthy men by sweating, nor could he prevent the alteration in double nephrectomized dogs by this means, for it occurred to him that the increase of the cryoscopic Δ of the blood, which occurs pathologically in renal disease, might be restored to normal by sweating.

Very extreme sweat processes may, as Leube (96) first showed, cause albumin to pass out in very small amounts in the sweat; at any rate, traces can be found in the sweat in many cases of nephritis.

Drugs such as mercury and iodine may reappear in the sweat. Kellermann (97) recently, using a new and well-tested method, has shown that the amount of iodine excreted in the sweat is negligible compared with that in the urine. Arloing (98) and Mavroyanis have described various toxic substances both in the sweat and urine.

Very little work has been done on the effect of baths upon *intestinal secretion*. Kowalski (99) claims to have discovered that hot baths increase the secretion of bile (twelve hours measurement). Short cold douches only cause a slight transient increase, and Kowalski sought to explain this as due to deeper inspiration and more viogrous contraction of the diaphragm.

Penzoldt (100), with reference to *gastric secretion*, has found that hot poultices or packs always induce a secretion of HCl, while cold baths delay its advent, and cause it to disappear prematurely.

Finally, the acidity of the gastric juice during and after vapour baths has been investigated. Simon (101) thinks he observed a marked decrease several hours after the vapour bath. Niether Edel (102) nor Du Mesnil (103) were able to confirm his observation.

VI.—LOCAL EFFECT OF BATHS ON METABOLISM.

Having so far treated only of the general effects, the action on circumscribed areas may now be considered. Local changes may be produced either by a direct change in the tissues caused by the temperature, or by some secondary changes dependent on anæmia or hyperæmia of the part. This latter question has had an entirely new light thrown over it by Bier's researches. It is known that cold is capable of great penetration, but that heat, since it increases the blood-flow, can penetrate less deeply; also that various temperatures seriously affect the metabolic processes, a subject which has been especially studied

in the nervous system. Biedermann (104) refers the enormous increase of reflex irritability in frogs exposed to cold to some change in metabolism, broaching the idea that there may be a different optimum temperature for anabolism and katabolism.

Von Frey considers that the nerves of frogs kept in cold water respond to the constant current, not as a direct effect of the cold, but from some alteration of metabolism caused by the cold.

Verworn (105) found that cold led to a storing up and diminished consumption of oxygen by the ganglion cells, while heat increased the consumption. Certain facts are known about the effect of temperature on the muscles—*e.g.*, a change in the contraction curve in the striped muscle of cold-blooded animals which Gad and Heymann described, and the change of *tonus* in the unstriped muscle, which is increased by cold and decreased by heat in both warm and cold blooded animals.

That heat can accelerate metabolism is shown by Penzo's experiment. Penzo exposed the two ears of a young rabbit to different temperatures, and found that the hotter one grew the faster. Practically, it is much more important to know that wounds kept warm heal more quickly, as Penzo and Bier demonstrated. This probably depends on hyperæmia rather than heat, for Liek (107) showed that division of the cervical sympathetic had precisely the same effect on wounds of the ear in rabbits [see also Bidder (108)].

The action of different temperatures on resorption is clinically important in treatment. Sassetzky (109) and Kossa (110) long ago observed that heat applied locally promoted the absorption and action of poison subcutaneously injected, while cold acted as a check. Klapp (111) found that when lactose was injected subcutaneously or intraperitoneally its absorption was retarded by cold and increased by warmth.

Hyperæmia, again, is of prime importance in this increased resorption due to heat, for Klapp (112), in his laparotomized animals, found that directly after removing the animals from a local hot bath the peritoneum, both visceral and parietal, was markedly hyperæmic. These experiments explain the long-known good effects of local hot baths on the abdominal organs. Bier's researches make it certain that hyperæmia can promote not only the resorption of fluids, but may assist in rendering soluble the more solid exudates.

So it appears that by altering the distribution of the blood-stream certain bathing processes may exert an influence upon the local metabolism.

VII.—THE EFFECT OF BATHS UPON THE DISTRIBUTION AND GENERAL STATE OF THE BLOOD.

This subject is rendered particularly complicated by the many hydrostatic and reflex vascular factors, which affect both the bulk and the flow of the blood. To unravel the many problems completely is a well-nigh impossible task One must be satisfied with saying that, except

for the direct effect on the abdominal organs mentioned above, there seems to be almost a conflict between the internal organs, especially the splanchnic area, and the integument for the possession of the blood; when the one is hyperæmic, the other is bloodless. Though this, of course, must not be read literally and without exception, still, we can take advantage of the fact by means of baths to improve the blood-supply and nutrition of the internal organs, which is so important a matter for their individual functions and for metabolism in general.

Not only is the distribution of the blood under the control, to some extent, of baths, but its general state may be affected. Cold, for instance, has considerable influence over the number of corpuscles per cubic millimetre. But it is quite certain that these variations are quite transitory, and although it is impossible to deny that metabolism is somewhat affected, the process cannot be one of long duration.

VIII.—THE EFFECT OF BATHS ON THE GENERAL WELL-BEING.

This is very directly related to the metabolism. Cold baths usually have a distinctly refreshing effect, while hot ones lasting for some time leave a feeling of fatigue. The former produces an inclination to muscular activity which the latter certainly impairs, and these general sensations have been verified by actual figures in an ergometric research by Vinay and Maggiore (113).

Very possibly these general feelings of briskness or fatigue are associated with the muscle-sense and with chemical heat regulation. As the result of cold, the muscles prepare as it were for defence, and severe heat loss causes a forcible impulse to movement; on the other hand, heat or disturbance produces a diminished capacity for work in the working organs, and as physical regulation, especially evaporation, fails, so a sense of fatigue comes on, accompanied as a rule by sweating.

Obviously, the secondary effects thus produced by far outweigh any direct action on metabolism, and constitute the main effect of baths on the metabolic processes in general. So that the problem becomes almost entirely one of variations in the individual for which exact tests and analyses can scarcely be conceived.

LITERATURE.

M. Matthes: Hydro-therapie. Cologne.
Bain and Edgecombe: Baths and Climate. London. 1905.
W. R. Huggard: Climatic Treatment and Balneology. London. 1907.
Weber: Climatotherapy and Balneotherapy. London. 1907.
1. Wick: Ü. die physiol. Wirk. verschiedener warmer Bäder und über das Verhalt. der Eigenwärme im allgemeinen. W. k. W. **1894.** Nr. 36, 37; and Beitr. z. klin. Med. u. Chir. **6.** 1894.
2. Kisch: Eulenburg's Realenzyklop. Article "Bäder."
3. Leichtenstern: "Balneother." in Ziemssen's Handb.
4. Riess: Ueber die Wasseraussch. des menschl. Körpers durch Haut und Nieren bei thermisch indifferenten Bädern. E. A. **24.** 65. 1888.
5. Oehler: Ueber die Hauttemp. gesunder Menschen. D. Ar. M. **80.** 245.
6. Rubner: Ar. Hy. **25.** 24.

7. Loewy: Ueber den Einfl. der Abkühlung auf den Gaswech. des Menschen. Ar. P. M. **46.** 189. **1890.** (Literature.)
8. Johansson: Ueber den Einfl. der Temper. in der Umgebung auf die Kohlensäureabgabe des menschl. Körpers. Sk. Ar. P. **7.** 123. 1896.
9. Rubner: Die Gesetze des Energieverbrauches bei der Ernährung. 1902. P. 220.
10. Speck: Die Physiol. der Atmung. 1892. P. 173.
11. Riethus: Über den Gaswechsel kranker Menschen, etc. E. A. **44.** 267.
12. Babák: Ueber Wärmeregul. des Neugeborenen. Ar. P. M. **89.** 154. 1902.
13. Liebermeister: Path. und Ther. des Fiebers.
14. Rubner: in Von Leyden's Handb. der Ernährungsther. **1.** 63.
15. von Jürgensen: Zur Lehre von der Behandl. fieberhafter Krankh. mittels des kalten Wassers. D. Ar. M. **4.** 1868. 323.
16. Ignatowski: Der Wärmehaushalt des Menschen nach Bädern und Duschen. Ar. Hy. **51.** 320. 1904.
17. Lefèvre: Topographie therm. après le bain. Ar. P. **5.** Série 10. 495. 1898.
18. Hirsch u. Müller: Beitr. zur Wärmetopographie der Warmblüter, etc. D. Ar. M. **75.** 267. 1902.
19. Rubner: Die Wirkung kurzdauernder Bäder und Duschen. Ar. Hy. **46.** 390. 1903.
20. Nasaroff: Über künstl. Abkühlung und Erwärmung warmblütiger Tiere. Ar. p. A. **90.** 482. 1882.
21. Durig u. Lode: Ergebn. einiger Respirationsvers. nach wiederholten kalten Bädern. Ar. Hy. **39.** 46. 1901.
22. Durig u. Lode: Ueber die Kohlensäureaussch. nach wiederholten kalten Bädern. Mü. m. W. **1900.** Nr. 4.
23. Sander Ezn: Der respirat. Gasaustausch bei grossen Temperaturveränderungen. Abh. d. k. sächs. Ges. math.-phys. Klasse. 1877.
24. Voit: Ueber die Wirk. der umgebenden Luft auf die Zersetzung. Z. B. **14.** 57. 1878.
25. Lépine et Floward: G. m. P. **1880.** 162.
26 Dommer: Ueber den Einfl. versch. Bäder auf den Eiweisszerfall. Z. M. **11.** 518.
27. Formanék: Ueber den Einfl. kalter Bäder, etc. Z. p. C. **19.** 271. 1894.
28. Strasser: Verhalt. des Stoffwech. bei hydriat. Therapie. W. K. **1895**; and Festschr. f. Winternitz. 1897.
29. Schilling: Beitr. zur Frage der Ammoniakaussch. D. Ar. M. **84.** 311. 1905.
30. Pflüger: Ueber Wärme und Oxydation der lebendigen Materie. Ar. P. M. **18.** 247. 1878.
31. Litten: Ueber die Einwirk. erhöhter Temperatur auf den Organismus. Ar. p. A. **70.** 10. 1877.
32. Simanowski: Über den tieris. Stoffw. unter dem Einfl. einer künstl. erhöhten Körpertemp. Z. B. **21.** 1. 1885.
33. Speck: Über den Einfl. warmer Bäder auf den Atmungsprozess. D. Ar. M. **37.** 1885; and Physiol. des menschl. Atmens. 1892. P. 173.
34. Voit: Ueber den Eiweissumsatz bei künstl. erhöhter Körpertemp. S. M., P. 120. 1895.
35. Winternitz: Ueber den Einfl. heisser Bäder auf den respirat. Stoffwechsel. K. J. **7.** 299. 1899.
36. Winternitz: Ueber die Wirk. verschied. Bäder, insbesondere auf den Gaswechsel. Habilitationsschr. Halle. 1902.
37. Ignatowski: Der Wärmehaushalt beim Menschen nach Bädern und Duschen von verschied. Temperatur. Ar. Hy. **51.** 319. 1904.
38. Salomon: Ueber die Wirk. der Heissluftbäder und der elektris. Lichtbäder. Z. d. p. T. **5.** 205. 1901.
39. Linser u. Schmid: Ueber den Stoffw. bei Hyperthermie. D. Ar. M. **79.** 514. 1904.
40. Bier: Die Hyperämie. 1906.
41. Loewy: Stoffwechselunters. im Fieber und bei Lungenaffektion. Ar. p. A. **126.** 218. 1891.

42. Baelz: "Bäder" in Stintzing-Penzold's Handb.
43. Hirsch u. Müller: Beitr. zur Wärmetopographie der Warmblüter. D. Ar. M. **75.** 287. 1902.
44. Naunyn: Beitr. zur Fieberlehre. B. k. W. **1869.** No. 4; and Ar. A. P. 1870.
45. Richter: Über Antipyrese, etc. Ar. p. A. **123.** 118. 1891.
46. Schleich: Ueber das Verhalt. der Harnstoffprod. bei künstl. Steigerung der Körpertemperatur. E. A. 1875.
47. Koch: Ueber die Aussch. des Harnstoffs, etc. Z. B. **19.** 447. 1883.
48. Formánek: Ueber den Einfl. heisser Bäder auf die Stickstoff- und Harnsäureaussch. S. W. A. **3.** 101. 278. 1892.
49. Topp: Ueber den Einfl. heisser Bäder auf den Organismus. Diss. Halle, 1903.
50 Bornstein: Ueber den Einfl. heisser Bäder auf den Stoffwechsel. D. m. Z. **1895.** Nr. 46.
51. Schulte Overberg: Ueber die Einwirk. hoher Aussentemp. auf den Glykogenbestand der Leber. Diss. Würzb., 1894.
52. Senator u. Richter: Ueber den Stoffw. bei Hyperthermie mit besonderer Berücksichtigung des Glykogens. Z. M. **1.** 54.
53. Martin: Ueber den Einfl. künstl. erhöhter Temper. auf die Art des Eiweissgehalts. E. A. **40.** 453.
54. Frey u. Heiligenthal: Die heissen Luft- und Dampfbäder in Baden-Baden. 1881.
55. Driver: Cit. in Lehrb. d. kl. Hydroth. v. Matthes. P. 87. 1903.
56. Lüthje: Ueber den Einfl. der Aussentemper. auf die Grösse der Zuckeraussch. K. i. M. P. 268. 1905.
57. Bendix: Ueber die Wechselbeziehungen zwischen Haut- und Nierentätigkeit. D. m. W. **1904.** 7.
58. Winternitz: Hydrother. auf physiol. und klin. Grundlage. P. 227.
59. Winternitz u. Pospischil: Über den respirat. Gaswechsel nach chem. und mechan. Einfluss. Bl. f. kl. Hydroth. **1893.** Nr. 1-5.
60. Paalzow: Ueber den Einfl. der Hautreize auf den Stoffwechsel. Ar. P. M. **4.** 492. 1871; and Diss., Bonn.
61. Jacob: Untersuch. über die Wärmequant. im Süsswasser, Salzwasser und kohlensaurem Stahlbade, etc. Ar. p. A. **66.** 1875.
62. Jacob: Gibt es hautreizende Bäder oder nicht? Ibid. **93.** 100. 1883.
63. Jacob: Qual. u. quant. Untersuch. der wichtigsten hautreizenden Bäder. B. k. W. **1877.** Nr. 16.
64. Röhrig u. Zuntz: Zur Theorie der Wärmeregul. und der Balneother. Ar. P. M. **4.** 57. 1871.
65. Köstlin: Ueber den Einfl. warmer 4 proz. Solbäder auf den Eiweissumsatz des Menschen. Diss. Halle, 1892.
66. Robin: La balnéation chlorurée sodique, ses effets sur la nutrition, etc. Bu. P. **1891.** 746.
67. Keller: K. S. **1891.** Nr. 8.
68. Heubner: Ueber Badekuren im Kindesalter. B. k. W. **1904.** Nr. 17, 18.
69. Hiller: Ueber die Wirk. der Seebäder. Z. M. **17.** Suppl. 257.
70. Loewy u. Müller: Ueber die Wirk. des Seeklimas und der Seebäder auf den Stoffw. 1904.
71. Bennecke: Ueber die Wirk. des Nordseebades. 1858.
72. Frankenhäuser: Einige neuere Gesichtspunkte für die Beurteil. des Nachwirkung der Bäder. B. k. W. **1903.** Nr. 28.
73. Schwenkenbecher: Das Absorptionsvermögen der Haut. Habilitationsschrift. Strassburg, 1904.
74. Zülzer: Die Sauerstoffaufnahme durch die Haut. Z. M. **53.** 403.
75. Senator u. Frankenhäuser: Zur Kennt. der Wirk. der kohlensäurehalt. und anderen gashaltigen Bäder. T. G. Nr. 1. 1904.
76. Nenadovicz: Die Wirk. der Franzensbader Moorbäder auf den Stoffwechsel. Z. d. p. T. **8.** 86. 1906.
77. Siegel: Über den Einfl. einiger Bäder und hydriat. Prozeduren auf die Oxydat. des Benzols im Organismus. Z. e. P. **3.** 351. 1906.
78. Coloman: Ueber den Einfl. der Hauttätigkeit auf die Harnabsonderung. E. A. **1.** 429.

79. Grefberg: Der Einfl. des warmen Bades auf den Blutdruck und die Harnsekretion. Z. M. **15.** 71. 1882.

80. Delezenne: De l'infl. de la réfrig. de la peau sur la sécrét. urin. Ar. P. **1894.** 416.

81. Wertheimer: De l'infl. de la réfrig. de la peau sur la circul. du rein. Ibid. **1894.** 308.

82. Lambert: De l'infl. du froid sur la sécrét. urin. Ibid. **1897.** 129.

83. Strasser u. Kuthy: Ueber die Alkalin. des Blutes und die Azidität des Harns nach therm. Einwirkung. Blätter f. kl. Hydrotherap. **1.** 1. 1896.

84. Krauss: Cit. by F. Kraus, Beitr. zur Lehre von der Säurenvergiftung. P. W. **1899.** Nr. 14. 170.

85. Araki: Ueber die Bild. von Milchsäure und Glykose im Harn. Z. p. C. **1892.** Nr. 16. 457.

86. Rem Picci: Ueber Albuminaussch. nach kalten Bädern. Bl. f. kl. Hydroth. **1902.** 3.

87. Donath u. Landsteiner: Ueber paroxysmale Hämoglob. Z. M. **1904.** 52.

88. Roque et Weil: Re. m. **1891.** Sep.

89. Igelranz et Déhon: L'Echo méd. du Nord. **1901.** 48.

90. Camerer: Ueber die chem. Zusammensetz. des Schweisses. Z. B. **11.** 271. 1901.

91. von Noorden: Ueber den Stickstoffhaushalt der Nierenkranken. D. m. W. **1892.** 35.

92. Köhler: Stickstoffaussch. und Diaphorese bei Nierenkranken. D. Ar. M. **65.** 542. 1900.

93. Strauss: Ueber die molekulare Konzentration des Schweisses. F. M. **1901.** Nr. 21.

94. Strauss: Ueber Nierenentlastung durch Schwitzen. D. m. W. **1904.** 34.

95. Bendix: Ueber Wechselbezieh. zwischen Haut- und Nierentätigkeit. D. m. W. **1904.** 5.

96. Leube: Ueber Eiweiss im Schweiss. Ar. p. A. **48.** 1. 1869.

97. Kellermann: Ueber die Aussch. des Jods im Schweiss. Z. e. P. **1904.** 1. 189.

98. Arloing: Soc. de Biol. de Paris. **1897.** 29 Mai.—Mavroyanis: Ibid. 6 Nov.

99. Kowalski: Ueber den Einfl. von äusseren hydropath. Prozeduren auf die Gallensekretion. Bl. f. kl. Hydrother. **1898.** 11.

100. Penzoldt: Die Magenverdauung des Menschen unter versch. physiol. physikal. Einflüssen. Festschr. d. Univ. Erlangen zur Feier des 80 jähr. Geburtstages des Prinzregenten. 1901.

101. Simon: Ueber den Einfl. der Dampfbäder auf die Magensaftsek. Z. M. **38.** 140. 1900.

102. Edel: Ueber den Einfl. des künstl. Schwitzens, etc. Z. M. **42.** 106. 1901.

103. Du Mesnil: Ueber die Einwirk. von Schwitzbädern auf die Azidität und Verdauungsfähigkeit des Magensaftes. Mü. m. W. **1901.** 22. 905.

104. Biedermann: Beitr. zur Kenntnis der Reflexfunktion des Rückenmarks. Ar. P. M. **80.** 408. 1900.

105. von Bayer: Zur Kennt. des Stoffwech. in den nervösen Zentren. Verworn's Zt. **1.** 265.

106. Penzo: Ueber den Einfl. der Temp. auf dei Regeneration der Zellen mit besond. Rücksicht auf die Heilung von Wunden. Mo. U. 1894. P. 107.

107. Liek: Ueber den Einfl. der arteriellen Hyperämie. Ar. f. Chir. **67.** 2.

108. Bidder: Hypertrophie des Ohres nach Exzision eines Stückes vom Halssympathikus. Ibid. **1874.** S. 97.

109. Sassetzky: Ueber den Einfl. erhitzter und herabgesetzter Temp. auf die Resorption, etc. St. P. **1880.** 15-19.

110. Kossa: Resorp. von Giften an abgekühlten Körperstellen. E. A. **36.** 120.

111. Klapp: Ueber parenchymatöse Resorption. E. A. **47.** 1901. 88.

112. Klapp: Ueber Bauchfellresorption. G. M. C. **10.** 254. 1902.

113. Vinay u. Maggiora: Über den Einfl. hydrother. Prozeduren auf den Widerstand der Muskeln gegen Ermüdung. Bl. f. klin. Hydrother. **1892.** 1.

114. Bain, Edgecombe, and Frankling: Lancet. 1905.

CHAPTER X

METABOLISM IN DISEASES OF THE DUCTLESS GLANDS

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I.—DISEASES OF THE THYROID GLAND.

The influence exerted by the thyroid gland on tissue metabolism has been demonstrated by observations made when this organ is diseased. When the thyroid fails in its function, there is a marked reduction in the total tissue changes throughout the body; when its function is carried on to excess, there is a considerable rise in the total tissue changes. The disturbance manifested in diseased conditions of the thyroid is chiefly qualitative; it is quantitative to a less degree. Perhaps excepting the muscles, no organ exercises so large an influence upon the body energy as does the thyroid. But although the ultimate "division of labour" in the body is not yet known, it is certain that this is not the only instance of the dependence of the tissues upon the function of a small gland. So great is the change wrought upon metabolism when the thyroid is diseased, that it is reasonable to assume that this gland has great influence over metabolic changes in the healthy state, though this is at present incapable of proof. We are not able to refer the changes in the metabolism of the resting state, whether studied in one person or in a set of persons, to the thyroid. Variations in the physiological activity of the thyroid are as yet unknown. In the healthy we can only study the influence exerted by the ingestion of animal preparations of the gland upon the body metabolism.

We shall first discuss myxœdema, then the effects of the administration of thyroid material to the healthy, and, lastly, the metabolic deviations which occur in Graves' disease.

A.—MYXŒDEMA.

Under the term "myxœdema" we shall include the true myxœdema of adults, cachexia strumipriva, and infantile myxœdema or sporadic cretinism. The picture of congenital myxœdema, based upon thyreoaplasia, is etiologically different from infantile and juvenile myxœdema. To collect these forms together under the name "sporadic cretinism"

appears to me permissible on account of convenience. In all three of these groups of cases the metabolic disturbances are similar. There are, however, some features distinctive of endemic cretinism which several authors, including Wagner, von Jauregg, and myself, consider to be closely allied to myxœdema, whilst others, as C. A. Ewald and W. Scholz, dispute the connection.

The Energy Exchange.

The gaseous exchanges are decreased in myxœdematous patients; they take little food and yet they gain weight. (No accurate estimate of food taken over a long period appears to have been made.) The low degree of tissue changes during the twenty-four hours is explained partly by the extraordinary bodily torpor and the minimal activity shown by the patient; moreover, the minimal requirements of the resting body are very small. They are diminished to a degree not seen in any other chronic disease. This only holds for patients in whom the disease is well marked. In four such cases the oxygen consumption fell to 50 to 60 per cent. of the normal. In three other cases, though the fall was insignificant, yet it reached a point below the normal minimum (Magnus-Levy).[1]

Disease.	*Age.*	*Height.*	*Weight.*	O_2.	CO_2.	O_2 *per Kg.*	*Relation of O_2 Excretion to the Normal.*
	Years.	Cm.	Kg.	c.c.	c.c.	c.c.	Per Cent.
1. Sporadic cretin ..	29	98·0	21·1	77·5	54·5	3·67	48
2. ,, ,, ..	14	84·0	15·8	72·6	59·4	4·62	60
3. ,, ,, ..	46	132·0	42·5	122·4	104·9	2·88	53
4. Cachexia strumipriva	29	133·0	32·4	103·2	83·9	3·19	58
5. Sporadic cretin ..	13	131·5	29·5	154·1	137·0	5·22	96
6. Myxœdema (adult) ..	21	158·0	59·1	210·0	166·3	3·55	94
7. ,, ,, ..	25	150·0	50·5	177·1	145·9	3·51	94

I have had little opportunity of studying severe cases of myxœdema in adults; but in view of the similarities existing between this disease and cachexia strumipriva, it is not unreasonable to expect a similar fall in the minimal metabolism in the former as in the latter. And it is probable that patients with severe endemic cretinism will react similarly.[2]

The Energy Exchanges during Treatment.

With the cure of myxœdema by organo-therapy the conspicuous fall in metabolism disappears. From being about 50 per cent. of the

[1] Andersson also found low CO_2 values in one severe case studied.

[2] In rabbits with ablated thyroids, Maier observed diminished gaseous exchanges. Baldoni noted the same in dogs. In cats Smith could not discover any changes, although Michaelsen records an increased CO_2 output (4). This was probably due, however, to acute tetany. In other points the conditions are not the same in animals with ablated thyroids as they are in the chronic myxœdema of man (5).

normal it often reaches the normal, or, if the administration of thyroid preparations be pushed, it may exceed the normal.[1] In three cases studied by Magnus-Levy the percentage increase in oxygen consumption amounted to 45, 66 and 72 per cent. respectively. The curve of increased oxygen consumption rises slowly during treatment, and, with the customary dose of one to three tabloids daily, reaches its height in three to four weeks. It remains at a steady height as long as a relapse is prevented. If the treatment be suspended, the curve of oxygen consumption slowly falls. In one of my cases, after a lapse of two or three months, the curve returned to the original low level. A second and third period of treatment produces a rise in the exchange of gases similar to the first.

In less severe cases of myxœdema, where the exchange of gases has been approximately normal, treatment is followed by a more moderate increase in the exchange—15 per cent. at most. These values may be also observed in the non-myxœdematous. The high values obtaining in the severe cases, and the low values in the milder cases, are easily explained. In the former set of patients, there being a complete absence of a substance which is necessary for metabolism, the result of the exhibition of the animal substitute for this substance is seen to its full extent. In the latter set a certain amount of this necessary substance is already present, therefore the changes induced by addition of the animal substitute are much less marked, and the effect of the treatment approximates more to that seen in health.

The Protein Metabolism.

The low state of energy exchanges corresponds to the low intake of food and the low nitrogen excretion. The excretion of urea often amounts to less than 20 grammes urea—*i.e.*, 8 to 9 grammes nitrogen.

If, as often happens when a patient is under observation, or investigations upon metabolism are being undertaken, the food intake is increased, nitrogen becomes easily stored up (3). This is readily understood if the experiment takes place during a period of retrogression. It was so with one of my patients during a second series of investigations. With a daily consumption of 8 to 10 grammes of nitrogen and 33 calories per kilogramme, in twenty-six days 45·6 grammes nitrogen (1·7 grammes per diem) were stored up, and the patient gained 2·7 kilogrammes in weight. In another series of observations, with the same number of calories ingested, there was a retention of only 0·4 gramme nitrogen daily. It is likely that part of the nitrogen is stored, not in the cells themselves, but in the tissues through which the morbid juices pass. When a liberal diet is continued, the output of nitrogen will probably equal the intake; otherwise the increase of weight would go on continuously.

During the exhibition of thyroid preparations the metabolism of

[1] In Andersson's work no figures are included. In the chronic myxœdema which occurs in ablated rabbits, Maier found an increase from the lowered minimal exchange after the administration of thyroid gland substance.

protein is radically changed. Mendel's patient before treatment excreted 14·3 grammes, and during treatment 20 to 36 grammes of urea daily. A patient of Zumbusch excreted 16 grammes before treatment, and during five successive weeks of the cure excreted an average of 18, 40, 33, 30 and 58·6 grammes per diem respectively. But in both these patients, as in the case reported by Napier, the diet was not fully analyzed (6). Such observations are thought to show that an " enormous increase of protein metabolism " takes place in myxœdema. But, critically examined, the figures of these authors only show that, given an increased appetite, there is an increased intake of food and a corresponding increase in food combustion. Properly conducted experiments, made immediately before the treatment and after its commencement, demonstrate that, *upon the same diet*, there is a loss of nitrogen (6). Ord's patient before treatment ingested 9·46 grammes of nitrogen daily and excreted 7·3 grammes, whereas during the first four weeks of treatment she excreted an average of 12·08 grammes, with an intake of 9·3 grammes. It should also be mentioned that the losses are greater during the beginning of the treatment. In one of my cases the first nine days showed losses of 1·1, 0·3, 1·0, 2·7, 1·8, 3·3, 2·9, 1·6, and 2·9 grammes respectively. In another series of observations, upon a patient who lost 28 grammes of nitrogen and 1·9 kilogrammes of weight during nineteen days, the losses diminished towards the end of the treatment, despite an increase in the amount of thyroid extract given. Still greater increase in nitrogen loss—7 to 9 grammes daily—were seen in a case studied by Widal and Javal, where, as a result of failure of appetite, the consumption of milk fell from 3 to 2 litres daily. The output of nitrogen can be diminished, but not quite abolished, if the total intake of calories [Magnus-Levy], or, better still, the intake of protein [Andersson], is increased.

A part of the excreted nitrogen, but only a part, is derived from the morbid material present in the tissues, for this disappears after a time. In only a few cases have the early nitrogen losses been absent at the beginning of treatment, as Ewald and Breisacher (7). But Ewald admits that during this period of the treatment the disease was not influenced. We may therefore consider him to have been dealing with nitrogenous equilibrium in a patient whose morbid condition persisted. Moreover, in a child aged two and a half years, a sporadic cretin under the care of Houghhardy and Langstein, it is stated that four weeks after the commencement of treatment nitrogen was retained. This, again, is not opposed to the above facts, for in this case no investigations were undertaken during the early weeks of treatment. The fact that a month after treatment was begun the child, already benefited and growing, should, with an increased intake of protein, retain nitrogen is as little remarkable as that a myxœdematous patient, during the later weeks of convalescence, should use and increase his musculature. Only the endemic cretins observed by W. Scholz showed no great changes in the protein metabolism when their thyroid dosage was increased to 8 tabloids daily. But, according to Scholz, probably no essential difference exists between myxœdema and endemic cretinism (7).

Individual Nitrogenous Constituents of the Urine.

The katabolism of protein, and especially urea formation, proceed regularly in myxœdema. Ord and White found that 80 to 86 per cent. of the nitrogen excretion occurred as urea; Haushalter and Guérin found it to be 85 to 87 per cent.; Widal and Javal, 92 to 95 per cent.; Houghhardy and Langstein, 81 to 84 per cent. The nitrogen excreted as ammonia in sporadic cretinism amounted to 4 to 6 per cent. [Magnus-Levy, Houghhardy and Langstein], and much the same figures were seen in the endemic form of the disease [W. Scholz]. A true acidosis apparently does not occur. Uric acid was several times found to be abnormally low. Mosler records 0·1 gramme; Magnus-Levy and Scholz, 0·3 gramme (corresponding to 1 per cent. total nitrogen); Haushalter and Guérin, on the other hand, found that 2·5 per cent. of the total nitrogen was excreted as uric acid. The amino-acid fraction is not larger than in health [Houghhardy and Langstein]. W. Scholz found increased xanthin bases upon one occasion in endemic cretinism. The low creatinin excretion (0·27 to 0·59 gramme) corresponded with the low weight of this observer's patients and with the low intake of meat foods (8). Treatment by thyroid preparations does not alter the proportions of nitrogen distribution to any extent; the authors already mentioned found similar figures during the administration of the drug. Only in the case of uric acid W. Scholz found, in two out of three cases, almost complete disappearance of this substance under treatment, the diet remaining the same (8).

The *quantity of urine* is small, often less than 1,000 c.c. daily. This probably depends upon the small amount of the total solids present. During treatment the amount increases, but not for any length of time, unless more fluid is taken. During the first week or two, however, the disappearance of watery myxœdematous deposits and the albuminous losses from certain tissues give rise to a slight increase of water; with a diet and intake of fluid absolutely the same as before treatment, the quantity of urine rises. This obtains also for the exhibition of thyroid extract apart from myxœdema (9). It is only temporary, and usually amounts to about 100 c.c. per diem. In a case of mine it rose 300 c.c. on the first day and 200 c.c. on the second. It soon returns to normal, especially as after a certain time the increased action of the skin takes a certain amount of the available water. In some cases there is no increase in the urine when the fluid intake remains the same [Byrom Bramwell in myxœdema, Th. Pfeiffer and W. Scholz in other diseases (9)]. Every pronounced and continued increase of urine presupposes an increase of fluid ingested. That in such cases the polyuria is primary is evident from the fact that in spite of increased fluid taken, both in the myxœdematous and in persons with healthy thyroids, thirst is frequently present during the administration of thyroid extract.

Sweat Formation.

In myxœdema, even when the body is exposed to great heat, no sweat appears; this feature is very characteristic. Of course, a certain degree of invisible sweating may occur. It is interesting to notice that the appearance of sweat on the surface of the body is nearly always the first sign of improvement. It often appears within a few days after treatment has been commenced.

Various Urinary Constituents.

Albumin occurs in the urine in 20 per cent. of cases. In one case, observed by Byrom Bramwell, the form of the protein present was serum globulin—there was no serum albumin (10). In another case the same observer found "a good deal of peptone" in the urine. Nucleoprotein was observed in a case by Guérin. It should be remarked that in animals thyroidectomy frequently leads to albuminuria and acute nephritis. But it must be remembered that in man albuminuria is not always a sign of serious organic kidney disease. In long-standing cases of myxœdema albuminuria is sometimes found to disappear quickly and permanently as the result of organo-therapy. It would seem, therefore, that in the course of the abnormal metabolism occurring in athyroidism substances are produced which irritate the kidneys without leading to a definite inflammation of these organs. But in a true nephritis, whether myxœdema be present or not, neither the albuminuria, nor the usual proportion existing between the serum-albumin and the serum-globulin excreted, nor the œdema, can be influenced in any way by thyroid feeding [Diebella and Illyes (10)].

The occurrence of sugar in the urine will be dealt with later.

Certain Salts.—The chlorine excretion may increase during treatment, as in the patient of Ord and White, in whom it rose from 1·7 to 2·1 grammes per diem. Such small amounts of increase as this may be derived from the disappearing pathological deposits present in the body. These same authors also observed a slight increase in the excretion of phosphoric acid. In my patient (2A), the diet being unaltered—although this diet was not analyzed with regard to the ash present—the total excretion of calcium, potassium, and magnesium remained nearly the same after as before treatment. The only thing noticed was that the amount of calcium excreted in the fæces increased at the expense of that in the urine. A similar observation was also made by W. Scholz (3) in two cases of sporadic cretinism. The explanation of this fact is not very clear, especially as Scholz observed (in the same patient) that the acidity of the urine was much increased during the stage of treatment.[1] In other conditions an increase in the acidity of the urine goes hand in hand with an increase of calcium excreted.

[1] But this increase of acidity does not always occur. Scholz found it again in a strumous boy, but I did not find it in a senile cretin, nor in an elderly myxœdematous patient, nor in a boy whose thyroid was healthy. Nor is the transfer of calcium above referred to always observed.

Houghhardy and Langstein's observations upon the retention of calcium and phosphorus in a case of infantile myxœdema are difficult of criticism, because the investigation was undertaken in a growing child and with a changing diet. I will only mention the fact that after treatment for four weeks with pronounced phosphorous retention relatively more phosphorus was excreted in the fæces than was the case before treatment was commenced. Moreover, the comparatively marked retention by the body of calcium in this case was probably explained by that growth of the bones which usually takes place in young cretins under treatment. The observation of Calabresi, who noted an increase in the excretion of chlorine and phosphoric acid during treatment of a myxœdematous patient, I have been unable to verify in the original.

The Degree of Food Absorption.

This is generally normal (7, 8). Upon rare occasions, despite the presence of constipation, a lowered absorption is noticed. Vermehren (3) observed a loss of 20 per cent. of nitrogen by the fæces, and Andersson (2) observed defective absorption as regards nitrogen and fat. In such cases the absorption improves with treatment. Rarely or never does a diminished absorption obtain with thyroid administration.

The Blood.

In about half the cases the number of red cells is diminished, usually only to a slight extent—*i.e.*, to three to four millions ; rarely to two millions or less [Buschan]. The hæmoglobin is sometimes diminished to a greater degree in proportion. But now and again high figures are found for both of these constituents of the blood. I have found as many as 5,600,000 red cells and 97 per cent. of hæmoglobin. It may have been in such cases as these last mentioned that Schneider found the specific gravity of the blood increased. In thyroidectomized animals a fall in the hæmoglobin, in the red cells, and in the oxygen affinity of the blood, often, if not always, obtains (11). Abnormalities in the size of the red cells are rarely found. Lebreton and Kraepelin found them increased to 10 metres in diameter. Ehrlich found their size diminished in sporadic cretinism, and Gottstein noted a similar change in a case of tetany associated with disease of the thyroid. With treatment these morbid changes tend to disappear, and in other respects also the condition of the blood improves.

It is certain that a definite relationship exists between the thyroid gland and the hæmopoietic tissues ; indeed, this relationship was for some time considered to indicate the only function of the thyroid. But the main affinities existing between these organs are exercised indirectly, and are not demonstrable by experiment. The observation of Zésas, Bardeleben, and others that a vicarious enlargement of the spleen takes place after thyroidectomy has been disproved (12). Nor is there any confirmation of the statement made by Zanda that the poison which acts in the body after thyroidectomy orginates in the spleen, and that therefore

the extirpation of this latter organ should do away with any need for thyroidectomy. Extirpation of the ovaries, or of the testes, has been shown to have no influence upon cachexia strumipriva in animals. The relationship existing between the thyroid and the pituitary body is probably much closer, for the latter gland has been found to enlarge in a few cases of thyroidectomy (12A). But the administration of pituitary extract cannot take the place of thyroid extract in the treatment of myxœdema.

The So-called "Mucin" of Myxœdema.

The characteristic doughy swelling of the subcutaneous tissues which occurs in myxœdema, and which is so different from ordinary œdema, was explained by early investigators [Stevenson and Halliburton (13)] by the presence of quantities of mucin in the tissues. These observers found, though not always, that in man and in thyroidectomized monkeys a larger amount of mucin was present than in health, especially in the skin, salivary glands and tendons. West also found increased quantities in the subcutaneous tissues. Harley attributes the increase of mucin in various organs to the increase in their connective tissues. A piece of skin excised by Jurgens showed a striking degree of "sliminess" on examination. On the other hand, Hunn and Prudden found the percentage of mucin in the skin to be normal.[1] Lebreton failed to find mucin in the blood of his patients (13). American authors take the view that the altered consistency of the subcutaneous tissue is merely due to the fact that ordinary œdema fluid is disposed in a different manner in myxœdematous patients and in cases of œdema proper—viz., in myxœdema it lies in the deeper and tense parts of the connective tiusse. Finding mucin in the secretions, in gastric juice, and in the urine scarcely proves anything [Buzdygan, Jurgens; Byrom Bramwell in one case found enormous quantities in the urine at the beginning of treatment], for catarrhal conditions are here very likely to complicate matters.

The nature of this substance, termed "mucin," is not definitely settled. Bourneville (13) examined the reducing power of the material after boiling, and found this absent. Although authors are not unanimous as to the increase of a substance precipitated by acetic acid, still the positive findings in this respect are important. Leaving out of account a few high values found in the examination of tendinous structures, it is worthy of notice that this substance appears in organs where it is absent in health. Halliburton found it in the blood of thyroidectomized monkeys, and—of more importance—in the parotid (up to 3 per cent.), in which gland there is no trace in healthy animals. Munk also proved in Mendel's case (6) the existence of mucin in parotid secretion. In some cases, therefore, it is clear that a pathological change in the chemical composition of the tissues can be demonstrated, and, judging by the few investigations made upon this subject up to date, this is a change which does not occur in other diseases to anything like the same degree [Halliburton (13)].

[1] The absence of mucin might in some cases be due to the fact that when the disease has been of long duration, and is fatal, the myxœdematous feature disappears. This has been proved with certainty in several cases.

B.—RESULTS OF THYROID FEEDING IN THE NON-MYXŒDEMATOUS.

The administration of thyroid extract to patients who have no symptoms of myxœdema causes changes in metabolism which are of a similar kind to those already dealt with, but these changes are less in degree. By the study of these patients whilst under treatment an effort has been made to find solutions to some theoretical problems, and in particular to trace the course of the changes in the various constituents of the body tissues. Of special interest is the problem of the increase of total oxidation in the obese.

The Nitrogen Metabolism.

This was found to be altered in nearly all cases observed when medicinal doses of thyroid extract were used. Many observations have been made upon non-obese (14) and upon obese (15) patients. The relative alteration in the nitrogen metabolism may amount to a loss of 5 grammes per diem on an average [Zinn]. Jacquet and Svenson found it rise as high as 7 grammes in one day. The losses are generally smaller than this, and they are found to diminish after prolonged use of the drug, especially in the obese [Magnus-Levy, Schiödte, and particularly Dennig]. If the diet has been ample before the observations were begun, and nitrogen has been on this account stored up, then no absolute loss of nitrogen may follow the administration. Nevertheless, even in these cases an appreciable diminution in the nitrogen gain by the body has been observed [W. Scholz, P. F. Richter, Th. Pfeiffer and W. Scholz, Zinn]. Compared with the myxœdematous individual, it may be said that the relative nitrogen losses are smaller in amount and shorter in duration in the non-myxœdematous. But in both conditions the gradual effect of the thyroid action on the nitrogenous exchange, and its persistence after the administration has been stopped, are very noticeable. It cannot be admitted that the protein metabolism of the obese is disturbed to a greater degree than in healthy patients, for a careful analysis of the observations made upon the two groups does not confirm this view. In each group some individuals show greater differences in the degree of their reaction to the treatment than others, and it is difficult to find satisfactory causes for these individual differences. It should be remembered, however, that the non-obese in these experiments generally received a full diet, whereas in one case at least—that studied by Zinn—an obese patient only received a third to a half of the total diet necessary for purposes of comparison. And as it happened that now and again in the obese the nitrogen losses were not larger, but were even smaller, than in persons of a normal build, it follows that the obese are no more prone to protein destruction as the result of thyroid treatment than persons with less rich reserves of material. In the two obese women observed by Magnus-Levy and Schiödte, who took the gland tissue without any ill-effects for several

weeks at a time, the nitrogen losses—at least, in the later period of the treatment—were exceedingly small (14, 15).

According to Vermehren, elderly patients (over fifty years of age) show a greater increase in their protein metabolism as a result of thyroid treatment than younger patients (especially children). This is attributed to an assumed diminution in function of the thyroid as age advances. Yet young patients are sometimes found to lose comparatively much nitrogen, and septuagenarians comparatively little [T. Pfeiffer and W. Scholz (15)]. Georgiewsky observed that young dogs reacted to thyroid extract more markedly than old ones (16).

Other Diseases.—Observations made upon patients suffering from simple goitre, osteomalacia, acromegaly, sarcoma of thyroid, tuberculous pleurisy, or paralysis agitans, have yielded results which do not differ appreciably from those obtained in healthy persons (17). When a cachectic condition is present, thyroid treatment causes nitrogen losses which are specially high [Schiff, David (17)]. Concerning the influence of thyroid treatment upon patients suffering from parenchymatous nephritis, see p. 988.

The influence of thyroid feeding upon protein metabolism is a direct one—that is to say, it is largely independent of diet. It does not disprove this view of the action of thyroid preparations—that with an increased number of calories ingested the nitrogen loss can be sometimes avoided [W. Scholz, P. F. Richter, and other authors]. For in these cases the amount of protein previously stored becomes less, and there is an equivalent fall in the amount of nitrogen lost to the body. It is significant, too, that protein loss occurs with thyroid treatment even when, upon a diet rich in fat, storage of fat takes place [Fritz Voit in dogs (18)]. It is tempting to attribute the increase in nitrogenous metabolism to the increase of total oxidation present; but in some cases the former is altogether absent, as in the obese female patient whom I investigated, and when the increase of nitrogen loss does take place it only becomes appreciable by the third or fourth week, whereas the change in the total oxidation processes is usually most marked during the first week. In support of this view of things, the observation of Andersson and P. Bergmann (18) may be adduced: that the excretion of nitrogen upon the second day of starvation, with the administration of iodothyrin, in spite of an unaltered excretion of CO_2, rose from 10·4 to 14·7 grammes (*i.e.*, more than the usual increase on the second day without the administration of the drug). Moreover, experiments upon nitrogen starvation (*i.e.*, in exclusive fat and carbohydrate diet) are in favour of this view [Andersson]. Although a larger increase of calories—and especially of protein—ingested during the continued use of thyroid, causes diminution in an existing loss of nitrogen, it does not altogether abolish it [Magnus-Levy and Andersson in myxœdema; Bleibtreu and Wendelstadt in the obese, with one good control investigation; Schiödte (18)]. But it is not possible to analyze all these experiments individually in this place, whichever way the results might tell.

Schöndorf, from his experiments on dogs, considers that a true loss of protein only occurs with great loss of flesh. This, however, is

certainly not the case in man. It is possible that during the first few days of the nitrogen loss an increased excretion of nitrogenous extractives (which alone were investigated by this author) plays a certain part. But, on the other hand, the sulphur and phosphorus excretion is often increased, and it is therefore certain, whatever the cause may be, that protein must have been lost also. Whether " thyrotoxin " has a special affinity for certain organs, or whether its katabolic action is exerted upon a form of protein in the body which is more labile and physiologically of less importance than the rest, cannot at present be decided.

The Nitrogen Distribution in the Urine.

This is as little altered by the exhibition of thyroid extract as it was seen to be in myxœdema. Only Israi, Vas and Gara have noticed a temporary increase of uric acid, and Dennig found a small increase of the urea nitrogen (an observation also made by Georgiewsky in dogs). Creatinin was noticed to be slightly increased by Th. Pfeiffer and W. Scholz (19).

The Excretion of Salts.

The excretion of chlorides rises in some cases [E. Roos in dogs; Ver Eeke, Israi, W. Scholz in man (1)]. This rise is usually small, however, and is followed by a retention of chlorine as if for readjustment. In the single starvation experiment of Andersson more marked increase was noticed (*i.e.*, 2 to 6 grammes of chlorine). The increase was, on the other hand, absent in some cases studied by Pfeiffer and Scholz (20). An increase of phosphorus excretion has been frequently observed, either in the urine alone [Roos, Andersson and P. Bergmann, Bürger, H. Senator], or, what is better evidence, in both the urine and fæces (20). According to Pfeiffer and Scholz the increase was absent after preceding phosphorus losses. The increase of phosphoric acid in the urine is sometimes fairly considerable—more than 1 gramme, as observed by Andersson and Bergmann, and by Burger. In other cases the increase appears to take place chiefly in the fæces [W. Scholz, A. Schiff]. In some instances [Fr. Richter] the phosphorus increase has been observed to be relatively much higher than the nitrogen increase, but it is impossible to say from which tissues this increase of phosphorus excreted is derived, as the physiological conditions are by no means clearly defined (20).

The excretion of sulphur frequently rises [Th. Pfeiffer and W. Scholz, Georgiewsky], according to Bürger, as high as 60 per cent., or much higher than the rise in nitrogen. In a second case, observed by Jaquet and Svenson, less sulphur was excreted in the urine with an increasing nitrogen excretion, but this is contrary to the usual occurrence.

The absorption of food materials is not altered in any appreciable manner by thyroid administration [values for protein, fat, and carbohydrates are given by L. Bleibtreu and Wendelstadt, Gluzinski and Lemberger, Zinn, Th. Pfeiffer and W. Scholz, Magnus-Levy, Grawitz, and others]. But rarely is a slight diminution noticed in the utilization of ingested fat [Jaquet and Svenson, Tikanadse (21)].

The Influence of Thyroid Feeding upon Metabolism.

In contradistinction to what occurs in myxœdema—in which the conditions are very different—the administration of thyroid gland tissue to healthy individuals is not regularly followed by any increase in the minimal metabolism. In three obese patients, and in one case of simple goitre, I found it increased ; in five other cases there was no increase (22). Positive results are recorded by Thiele-Nehring, as well as by Stüve (22). Just as in myxœdema, the increase (when it occurs) develops slowly during the course of two to three weeks. With moderate doses of the drug the increase did not exceed 15 to 25 per cent. The effect is less marked when small doses are given and slowly increased than when large doses are given at first. Jaquet and Svenson found that no increase occurred in the exchange of gases in two obese patients whilst under treatment. The same result was seen in investigations carried out during fasting for a period of five to ten days, and Andersson and Bergmann confirmed these last experiments by observations of less duration.

I am of opinion that the view may be accepted that the administration of a substance originating in the healthy body is able (in some persons, at least) to increase the metabolic changes normally going on in the tissues. This view is not held by Andersson and Bergmann, nor by Speck (22). The much more striking results seen in myxœdema, as well as (to a less degree) in Graves' disease, confirm this view. The reason why only some, and not all, healthy persons show this reaction to thyroid feeding is at present as little understood as the reason why similar individual differences in reaction are seen in cases of myxœdema (23) and in cases of Graves' disease. The explanation is certainly not that the difference in reaction is due to any difference in the kind of preparation used. For, in some cases, a large dose produces severe toxic symptoms, occasionally even leads to an appearance of acute Graves' disease [Gautier, Notthafft, and others] ; whereas in other cases very large doses may be given without anything untoward occurring [Becker gave a child 90 tabloids in one day, and Janike gave a patient 4,000 tabloids in the course of six years (23)]. The real reason is undoubtedly bound up with the individual reactions of the patient's tissues.

With the small amount of data at present available it cannot be held that the exhibition of animal thyroid leads more easily to increase of tissue changes in obesity than in normal persons. It might readily be understood that this is the case if there were evidence forthcoming that tissue changes are relatively less marked in obese than in normal persons, but such evidence is lacking. Moreover, no proof as yet exists that the thyroid function is defective in obesity.

Any increase of the total tissue changes in obesity during thyroid treatment is too inconstant to explain the undoubted loss of fat which occurs in some cases. And a critical survey of the various investigations made in this direction [amongst others by L. Bleibtreu and Wendelstadt (24)] leaves no doubt that occasionally, with an unaltered diet, increased loss of fat does sometimes result from thyroid treatment. But

an increase of the total changes amounting to 20 per cent. would, in an obese patient of 100 kilogrammes, only mean an increase of 400 calories, necessitating a fat consumption of but 42 grammes per diem. And in cases where, with unaltered diet, a real, and not merely apparent, increase in fat loss occurs, the influence of increased exercise must be taken into account. This influence has been demonstrated to be not inconsiderable in animal experiments [Fritz Voit showed it to be present to the extent of 20 per cent. of CO_2 in a dog, and Bloch obtained comparable results in rabbits (24)].[1] The response to stimuli normally shown by phlegmatic persons may increase as the result of an increase of their nervous force (induced by such drugs as thyroid), and these persons may thus be incited to more energetic movement, even though their occupation be apparently unchanged. When this factor is excluded, as in one of my cases, confined to bed on account of old hemiplegia, the loss of fat through thyroid feeding does not occur.

C.—GRAVES' DISEASE.

In those investigations upon Graves' disease when the food intake has been accurately determined, considerable increase of the total metabolism has been observed in several cases [Fr. Müller (26) and others]. This is partly explained by the tremors and by the restlessness, which are often such marked features in the disease. But the minimal metabolism is also increased [Magnus-Levy, Stüve, H. Salomon (27)]. In eight serious cases I found, without exception, an increase in the oxygen consumption ; in four mild cases this increase was not observed. Patients with simple goitre show no increase in their gas exchanges [Stüve, Magnus-Levy].

Case.	*Observer.*	*Age.*	*Height.*	*Weight.*	O_2.	CO_2.	O_2 *per Kg.*	*Percentage of the Normal.*
		Years.	Cm.	Kg.	c.c.	c.c.	c.c.	
1. Acute	Magnus-Levy	20	158	50·7	348·9	295·0	6·89	About 170
2. Severe chronic		26	150	50·5	344·0	236·2	6·80	„ 170
3. Severe ..		22	161	55·1	305·8	256·2	5·55	„ 142
4. Slight		55	156	43·9	266·9	219·3	5·31	„ 122
5. Slight		20	148	45·0	213·2	181·1	4·74	„ 105
6. Operation ten years previously		40 (?)	171	84·0	282·8	241·1	3·37	„ 100
7. Simple goitre		36	162	51·5	176·7	134·1	3·43	„ 90
8. Four severe cases of Graves' disease	Salomon	—	—	53 to 56	—	—	6·9 to 7·15	—

[1] Schöndorff estimated the increase of total oxidation during a prolonged period of abundant thyroid feeding in a dog to be 35 per cent. So careful are this author's calculations, and so long-continued were his observations, that I cannot consider the results to have been other than as stated. In the case of man similarly reliable observations do not exist. The most careful and the most prolonged investigations in the obese with thyroid treatment are those of Magnus-Levy. In Schiödte's still longer observations the figures for the nitrogen balance are perhaps scarcely so reliable.

The great increase in oxygen consumption—sometimes as much as 50 and even 70 per cent.—which is to be seen in bad cases of Graves' disease occurs nowhere else in the whole range of pathology, not even in high degrees of fever, nor in leuchæmia, nor in diabetes. A small part of this increased oxygen consumption may be due to increased cardiac and respiratory action, and perhaps in some cases an increased ingestion of food may be a factor. (The first patient in the above table ate daily 230 grammes of protein, or 5,500 calories.) In a critical survey of the subject Speck (28) is led to attribute the remainder of this increase of oxygen to the pronounced tremors which are a feature of the disease. According to this author the metabolism of the tissues at rest is not increased. That continuous tremors do lead to an increase of the gas exchanges must be admitted; I have myself found the consumption of oxygen increased by 20 to 30 per cent. in paralysis agitans. But the cases of Graves' disease which I investigated showed no tremors whilst they were kept at absolute rest. And the observations made whilst the patients were asleep, either naturally or as the result of morphia, showed no diminution of the oxygen consumption as compared with those made whilst the patients were awake. Hyoscine, which checked the tremors in paralysis agitans, and thereby reduced the gas exchanges to their normal level, showed no such influence upon the exchanges of patients suffering from Graves' disease. Upon these grounds I maintain very strongly that in Graves' disease the gas exchanges during rest are increased. The facts observed in myxœdema, where the exhibition of thyroid extract causes the abnormally low gas exchanges to return to their usual level, lend strong support to this view.

This striking increase in the gaseous exchange seen in severe cases of Graves' disease is, from the point of view of metabolism, a most important argument in favour of Möbius's view of this disease—that it is due to an increase in the function of the thyroid. And those authorities who do not accept this view, but who base their notion of the pathology of the disease upon lesions in the central nervous system, must admit that many of the symptoms of the disease depend immediately upon changes taking place in the thyroid. The morbid state of the thyroid certainly dominates the clinical picture. Mikulicz expresses the same notion when he speaks of the thyroid as intensifying the morbid phenomena occurring in the disease; this view, however, scarcely lays sufficient stress upon the importance of this organ as a cause of the morbid phenomena.

When pronounced and lasting improvement takes place in a case of Graves' disease, the gaseous exchanges sink, not only relatively in respect to the weight, but absolutely. The body, once more rich in protein and fat, consumes absolutely less oxygen and excretes less carbon dioxide than before [Magnus-Levy (27)]. The following figures show the mean of sixteen observations made during a period of ten years upon the same patient:

1895: 45 kilogrammes, 341·1 c.c. O_2, 188·4 c.c. CO_2, 5·35 O_2, 4·18 CO_2 per kilogramme per minute.

1896: 50·3 kilogrammes, 209·8 c.c. O_2, 157·1 c.c. CO_2, 4·09 O_2, 3·07 CO_2 per kilogramme per minute.

On the other hand, if the patient gets worse, a still greater increase in the gaseous exchanges is noticed. In one case reported by Hirschlaff (29) I noticed a consumption of oxygen which varied but little in six weeks, the mean being 349 c.c. per minute. In the last few weeks before death this figure rose to 385, 405, and 446 c.c.

I was able to study the influence of the amount of food intake in the first of the cases mentioned in the table on p. 995. On the first and second day after a breakfast which was admittedly abundant in amount the oxygen consumption had risen to 75 c.c.—*i.e.*, 22 per cent. more than the usual figure in this particular case. This effect is similar to that seen in health under the same conditions.

The Influence of Certain Drugs.—Seeing that thyroid feeding in Graves' disease often leads to an exacerbation of the symptoms, it might be expected that a corresponding increase in the gaseous exchanges would occur under this treatment. However, I seemed to miss this effect in two cases which I studied—in the first case probably because the feeding with thyroid only lasted five days ; in the second because the patient's condition, in all clinical respects uninfluenced by the drug, was already improving. Feeding with thymus extract for longer or shorter periods was found to be without any such effect in Stüve's case, as well as in one of my own (27). H. Salomon treated a patient with " rhodagen " and another with Möbius's antithyroid serum ; the clinical effects were slight, and the gaseous exchanges remained unaltered. Moreover, the daily administration of 40 grammes of sodium bicarbonate for a period of five days, and of 1 gramme of hydrochloric acid for one day, were quite devoid of any influence upon the oxygen consumption [Magnus-Levy]. I mention this experience because it has been stated that a different result has been obtained by the use of large doses of alkalis (27).

The extraordinary degree of emaciation sometimes noticed to occur in Graves' disease—instances where patients have lost half their weight in one year have been described—cannot be explained solely by an increase in the body requirements during rest, although this is occasionally enormously raised. In the first of the series of cases already referred to I estimated the fundamental tissue changes during one day as 2,300 calories. Over and above this the total metabolism is increased by the tremors, and by the marked restlessness of these patients. In spite of increased appetite, the ingesta remains less than the excreta, and great reduction of weight occurs. Of course, this is still more marked if anorexia be present. In only a few cases, where very large quantities of food are given, is a loss of weight absent during the height of the disease ; it is still rarer to find an actual superalimentation occurring (29).

The Protein Metabolism.

G. Lustig (30) was the first to call attention to the increase of nitrogenous metabolism in Graves' disease. But this author's figures seem to me to prove little more than that his patients had larger

appetites, and consumed and stored up more protein than the healthy control.[1]

It was Fr. Müller (30) who first published convincing figures. Müller's patient, who was reduced in weight to 30 kilogrammes, in spite of a daily intake of 10·5 grammes of nitrogen, lost 0·94 gramme daily during an acute exacerbation towards the end of the illness. Another patient, confined to bed, would certainly have stored protein upon the diet given if he were healthy (1,689 calories or 58 calories per kilogramme of body-weight). A patient of Matthes (30), weighing 64 kilogrammes, upon a daily diet of 12·9 grammes of nitrogen (40 calories per kilogramme), lost 3 grammes of nitrogen daily. In other cases Matthes succeeded in obtaining nitrogenous equilibrium, but only after giving enormous quantities of protein. In the case of three patients whose weights varied from 51 to 61 kilogrammes it was necessary to increase the food nitrogen to 15·9 to 19·1 grammes daily (39 to 44 calories per kilogramme), and these figures were exceeded in still another patient, who consumed an equivalent of 22 grammes of nitrogen (50 calories per kilogramme). One of my patients, despite an intake of 62 calories per kilogramme, continued to lose weight. And all these cases were far advanced in the disease and confined to bed.

Such an increase in the consumption of protein, however, must not be expected always in ordinary cases of chronic Graves' disease. As in other diseases of long duration, it is particularly during the periods of acute or subacute exacerbations that the protein metabolism is increased and that stored-up material is utilized. Along with the improvement in the clinical condition the weight increases and protein is retained. Matthes' patients were considerably ameliorated by partial thyroidectomy. Three to four weeks after the operation, upon the same diet as before it, the nitrogen balance showed an increase on the side of storage in all cases up to 2 to 4 grammes daily. Even after two months, when the weight and the protein metabolism were good, the patients still retained a similar quantity of nitrogen when put upon the same dietary.

Scholz investigated a case during the progressive period of the disease (30). The condition of his patient varied considerably. In the first four weeks under treatment she lost $3\frac{1}{2}$ kilogrammes, but regained 5 kilogrammes during the following three weeks. There was a daily retention of 7·4 grammes nitrogen on an intake of 21·5 grammes nitrogen. The dietary provided 47·7 calories per kilogramme—quite an excessive amount.

[1] Two healthy and two sick women were placed on the same food intake. The urinary excretion was as follows:

	Urea.	P_2O_5.	*Cl.*
	Gm.	Gm.	Gm.
Patients	33·9–25·2	2·0–1·6	12·1–16·4
Normal women ..	21·3	1·3	9·1

When the figures were taken day by day, the several constituents varied enormously, as much as 100 per cent. from one day to another.

During the worst periods of the disease nitrogen loss is by no means always the rule. Matthes employs a liberal diet in these cases, and this is quite possible, for the appetite is usually good. Kocher records the following figures from advanced cases: urea, 34 grammes (16·5 grammes urea nitrogen), a quantity corresponding to 20 grammes total nitrogen. This is a very high output, particularly when it is remembered that the intake of meat is usually not large in this condition.

Bulimia has been observed by many clinicians (31). The most instructive example is afforded by Hirschlaff's observation (31) of a patient with subacute Graves' disease. During a series of investigations lasting for forty-six days this patient consumed a diet consisting of the enormous amount of 220 to 240 grammes of protein, 500 to 550 grammes of carbohydrate, and 217 to 273 grammes of fat per diem (5,070 to 5,650 calories, equivalent to 100 to 120 calories per kilogramme). The patient's weight rose from 41·7 to 53·5 kilogrammes, and there was a daily gain of nitrogen of about 4 grammes.[1] Of the total gain in weight, about 5½ kilogrammes were disposed as "flesh" and 6 kilogrammes as fat. But in spite of this successful superalimentation, the disease process became worse, and the patient died during her stage of superalimentation of acute exophthalmic goitre.

I think the question whether the protein losses occurring in Graves' disease result only from the condition of relative subalimentation, or whether they are to be ascribed to the disease itself, should be answered in the latter sense. Sometimes, at least, a deleterious influence is exerted by the disease upon the protein metabolism. To establish a state of nitrogenous equilibrium it is necessary not only to increase the intake of calories enormously, but specially to increase the intake of protein much more than in health. When a loss of protein occurs in disease independently of a diminution of the diet, it is usual to designate this loss as of "toxic" origin. This is also the customary explanation in Graves' disease. But by this term "toxic protein disintegration" it must not be meant that such a process is invariable, and that it cannot by any means be avoided. Indeed, May (32) has shown, by his experiments upon animals suffering from fever, that loss of protein can be prevented. And other observers have proved the same thing in Graves' disease, especially where a state of superalimentation is induced.

The Urine in Graves' Disease.

Quantity.—Polyuria is occasionally noted [Möbius, Buschan (31)]. In some cases, as in that of Hirschlaff (29), where 5 litres of urine were passed daily, this condition is explained by the abundant ingestion of fluids which was part of the superalimentation taking place at the time (the patient was taking 3 litres of milk daily). In other cases, where the amount of urine reached 10 litres or more, certain neuroses or diabetes insipidus have been dealt with; the polydipsia is in these cases associated with great thirst.

[1] In estimating the figures the value of the nitrogen losses in the sweat are only assumed.

The Nitrogenous Constituents of the Urine.—According to Daddi (33), the relative *urea* content is the same as in health, and the same may be said for the *ammonia*[1] [Magnus-Levy]. *Uric acid* was found relatively normal in quantity by Schreiber and Waldvogel, Magnus-Levy and R. David (34)—from 0·4 to 0·6 gramme. A solitary instance of increased excretion of uric acid (5·0 grammes) is recorded by A. Kocher (30), perhaps due to the therapeutic use of thymus gland. No variation in the form of katabolism of the protein and nuclein molecules is known to occur.

Albuminuria is uncommon (35). In some cases transient albuminuria has been described [Bramwell (25), Kocher]. Two of Bramwell's cases showed persistent albuminuria, increasing in degree, but no casts, and no clinical evidence of nephritis. Chvostek's (36) observation that an excretion of "peptone" (? albumoscs) occurred in a patient suffering from Graves' disease after an ingestion of 150 to 200 grammes of grape-sugar deserves confirmation. Boinet and Silber (37) have isolated three "*ptomaines*" from the urine of patients the subjects of Graves' disease, which, injected into animals, produced symptoms allied to exophthalmic goitre. These and some other "ptomaine" observations have been received by German authorities with some reserve, perhaps justly so.

For *glycosuria*, see p. 1003 *et seq.*

Acetone was found in the urine in small quantities (1, 2, to 4 centigrammes) by Schreiber and Waldvogel (38). Larger amounts of acetone bodies may occur under similar conditions to those leading to excretion of these substances in other diseases—as, for instance, in connection with relative deficiency of carbohydrates. Thus Dreschfeld (38) found aceto-acetic acid present in a patient with nervous vomiting.

An increased excretion of *indican* is rarely noted. Marked putrefactive changes in the intestine are not a feature of the disease.

The *utilization of food* in the bowel is good, even when the stools are somewhat soft, which they not infrequently are (33).

The following table shows the loss :

Carbohydrate.	*Nitrogen.*	*Fat.*	*Observer.*
5·2 per cent.	8·2 per cent.	8·9 per cent.	F. Müller (26).
—	6·8 ,,	—	W. Scholz (30).
6–8 per cent.	8·0 ,,	12·9 per cent.	Hirschlaff (29).

To what degree assimilation is affected by persistent and serious diarrhœa has not yet been investigated.

[1] In Hirschlaff's case (29), already referred to, I found that with a total nitrogen excretion of 24 to 30 grammes, 0·8 to 1·3 grammes were present as ammonia—*i.e.*, 3 to 4 per cent. These observations extended over a period of thirty days. After a daily administration of 1 gramme of hydrochloric acid for five days, the ammonia rose to 1·85 grammes. With an intake of 40 grammes of sodium bicarbonate it immediately sank, and on the fourth day it had fallen to 0·04 gramme, and to 0·0 gramme on the fifth day. I have found the amount of ammonia also normal in a second case.

The Constituents of the Ash.

Upon the chlorine balance there are no observations. But an increased excretion of *chlorine*, as compared with health, occurred in two of Lustig's patients (30), and was evidently owing to increased chlorine ingested. W. Scholz's figures (6·8 grammes NaCl) do not call for any comment; the excretion varied but little upon individual days (30).

Nothing is known about the excretion of *sulphur*, either the amount excreted or the sulphur balance. But the katabolism of sulphur varies as little from the normal as does that of the nitrogenous principles. Daddi and Marchetti (33) found the relations of ethereal to inorganic sulphates, and of neutral sulphates to total sulphates, were normal.

Scholz noted a daily retention of 1·06 grammes of *phosphorus* with the comparatively low intake of 2·8 grammes P_2O_5. This gain of phosphorus corresponds approximately with the gain in nitrogen (7·4 grammes), and of itself calls for no remark. The only abnormal feature in connection with the phosphorus excretion was the distribution of it by the two channels, urine and fæces: of 1·75 grammes P_2O_5 excreted, 1·42 grammes passed out by the urine, and only 0·33 gramme by the fæces (*cf.* the alteration observed after administration of thyro-iodin, p. 1002). This figure for the excretion of the fæces is very low, and is not seen with a similar diet (including much milk) in health. A patient of Daddi and Marchetti (33), however, behaved differently. No figures and no clinical details relating to this case are to hand, but according to the abstract of these authors' observations, no phosphorus was retained, and the phosphorus was excreted in increased amount by the intestine.

The Sweat.—Although many patients excrete large quantities of fluid, of urea, and of sodium chloride, by means of their sweat glands, no measurements or other investigations have been undertaken in this direction. This is an important field for research, for sweating is so marked in the disease that it has been known to continue *pari passu* with an associated severe diabetes in the same patient, and the sweat in these circumstances may contain sugar [C. Hannemann (39), Max Schmidt (39)].

The Blood.—No specific changes usually occur in the composition of the blood. The percentage of hæmoglobin rarely sinks below 80. Neither anæmia nor hydræmia is common (25, 26, 40).

The Influence of Thyroid Feeding upon Metabolism in Graves' Disease.

The exacerbations produced in the symptoms of Graves' disease by the exhibition of thyroid substances, though ofttimes noticed, have only to a slight extent been studied, especially in regard to metabolism. For some reason or other, those cases in which observations have been made showed no marked clinical disturbances, either because the patients

were refractory to the drug, as is sometimes the case, or because the treatment was of too short a duration.

Concerning the *exchange of gases* see p. 997.

The Balance of Nitrogen.—In two patients observed by Scholz (30) and Hirschlaff (29) the marked nitrogen gain of the preliminary period was not disturbed in the slightest by the daily exhibition of four tabloids of thyroid extract. On the other hand, a patient of Matthes (30), who was given by mouth her own excised thyroid gland (dried), responded to this treatment by an increased nitrogen excretion of 1 and 2 grammes on the second and third days respectively. A patient of David's (17), evidently a bad case, after taking three to five tabloids of thyro-iodin, excreted 90 per cent. more nitrogen than previously whilst taking an exactly similar diet.

I found the *ammonia* content of the urine in Hirschlaff's (29) case was as high during the period of thyroid feeding as before. Nor is the quantity of *uric acid* found to be influenced [Schreiber and Waldvogel (34), David (34)]. The *assimilation of protein* remained unaltered [Scholz, Hirschlaff]; so, too, did that of fat [Hirschlaff]. The excretion of *sodium chloride* rose from 6·8 to 8·7 grammes [Scholz].

In the case of *phosphoric acid* alone is a change, and that a surprising one, recorded. Scholz's (30) patient, who, during the preliminary period of observation, had stored up 1·06 grammes P_2O_5 (p. 1001), lost daily during the period of thyroid exhibition 2·09 grammes, and this striking increase of phosphorus excretion took place almost exclusively by the bowel.

	P_2O_5 *Ingested.*	P_2O_5 *Excreted.*		*Balance.*
		Urine.	Fæces.	
	Gm.	Gm.	Gm.	
Preliminary period ..	2·8	1·42	0·33	+1·06
Period of feeding with thyroid	2·8	1·49	3·42	−2·09
Difference.. ..	0·0	−0·07	−3·09	−3·16

It is true that Roos (5), and later several other observers, found an increase in the excretion of phosphoric acid (partly by the urine, partly by the fæces) when feeding animals with thyroid extract. But in none of these did such a marked change in the behaviour of the phosphorus excretion occur as in Scholz's patient. It is highly desirable to repeat this observation in other cases. Until that has been done it is hardly possible to conclude that in Graves' disease there is a special facility observed in phosphorus katabolism.

D.—THE RELATIONS OF THE THYROID TO CARBOHYDRATE METABOLISM.

These relations, which were perhaps somewhat over-rated formerly, have been of late more correctly estimated. They consist chiefly in the liability to glycosuria if large amounts of thyroid secretion are active in the body.

This state of things is most apparent in Graves' disease. Not at all rarely it leads to diabetes mellitus. According to Hannemann, at least twelve of the older cases observed belong to this category, and according to Naunyn a few more (43). Naunyn adduces another case recorded by Schmitz, and Grube and Bettmann one each. I have also found two short notices of this condition by Schreiber and Waldvogel, and by H. Salomon, and a more detailed account of a case by Grawitz (43). Von Noorden observed diabetes with Graves' disease four times. Kocher found spontaneous glycosuria present in two out of fifty-nine cases of Graves' disease. Instances of severe diabetes are certainly rare; the occurrence of diabetic coma has only been recorded twice, by Budde and by Hannemann (43). In the urine of the latter case I found large quantities of acetone, aceto-acetic acid, and oxybutyric acid. To which type these relations between Graves' disease and glycosuria or diabetes belong—whether hepatic or pancreatic[1]—it is at present impossible to say.

Considering how common a disease exophthalmic goitre is, the addition of diabetes to the symptomatology is comparatively rare. And the tendency to this complication, evidenced by the ready occurrence of alimentary glycosuria, is not so marked as was once thought. After Ludwig and Kraus (44) observed it for the first time, Chvostek found it present in five out of eight cases.[2] Later observations have shown the frequency to be much less than this (Strauss found it in only three out of seventeen cases, and Zülzer, Friedheim, Naunyn, Magnus-Levy, and Kocher found it absent altogether, or only occasionally present). Von Noorden believes it to occur only in severe and progressive cases of Graves' disease (44).

Apart from myxœdema, a series of cases have been noted in which the use of thyroid extract has led either to true diabetes or to a transient glycosuria, or to an easy production of alimentary glycosuria. True diabetes coexisting with myxœdema has been observed by Ewald (7),

[1] Direct relations existing between the thyroid and the pancreas, assumed by Lorand on account of histological and pathological investigations, have not been proved. In face of the appearance of alimentary glycosuria after thyroid administration, the action of the liver must be first considered. In experiments upon dogs, Georgiewsky found sugar was excreted after thyroid feeding only when he had given large quantities of carbohydrates—that is, when the storage of glycogen was considerable. Porges (44A) found that lævulose was excreted by a dog fed with thyroid after giving large quantities of cane-sugar. The point of special moment is, not the nature of the sugar secreted (for lævulose may also appear in the urine of dogs fed with much cane-sugar without the exhibition of thyroid), but the long duration (seventeen days) of the lævulosuria after cessation of the thyroid feeding.

[2] Chvostek found a polysaccharide present in the urine of one patient.

with acromegaly by Lorand (45). Transient glycosuria extending over a period of nine days was noted by Dale in a case of psoriasis, and in other cases by Notthaft, Dennig,[1] von Noorden and Friedheim (46). Alimentary glycosuria has been noted by Mawin, H. Strauss, Bettmann, von Noorden, and many others (47). From a consideration of the investigations and views of several authors upon the subject, it may be assumed that the thyroid gland, when it leads to the excretion of sugar, acts as an inducing cause wherever a predisposition to glycosuria exists. This certainty holds for Lorand's case of acromegaly and for the cases of obesity observed by von Noorden, Dennig, Notthalt, Friedheim, and others. Here the glycosuria was latent or of temporary duration (see a very clear case described by Friedheim). Grawitz (43) has reported a very conclusive instance of the increase which may occur in an existing glycosuria by means of thyroid exhibition in diabetes. The sugar was increased from 40 to 80 grammes over a long period.

The cases of alimentary or of spontaneous glycosuria occurring without a demonstrable tendency to this condition are quite rare. The occurrence of them is nothing like so common as would appear from the researches of Bettmann, for instance, where they are stated to comprise 48 per cent. of his skin patients. Mawin found them present in only 8 per cent., and Strauss only found the condition in 20 per cent. of nerve cases, in whom there is naturally a tendency to alimentary glycosuria. The occurrence of spontaneous glycosuria, to which, since Ewald's writings, the attention of most authors has been directed, is, apart from "latent diabetes," certainly very uncommon (46, 47).

In contradistinction to the fall in the limit of assimilation of sugar which occurs in Graves' disease, a rise has been looked for in myxœdema. Hirschl (48) did not reach the limit in two of his patients by giving 200 grammes of grape-sugar, nor, in a third case, even with 500 grammes. This may possibly be explained by the tardy intestinal absorption present in myxœdema. Knöpflmacher (48) has confirmed Hirschl's results in cases of sporadic cretinism, and has shown that the limit of sugar assimilation sinks to the physiological level as improvement takes place under treatment by thyroid.

It may be concluded from all the observations hitherto obtained that an increase of thyroid activity in the body makes the normal use of carbohydrate more difficult; or, putting this result more accurately, it makes an absolute retention of sugar in the tissues less easy. In face of this it is remarkable that glycosuria occasionally occurs in untreated cases of myxœdema [Campbell, Jürgens, Byrom Bramwell, Magnus-Levy, Luxemburg (49)]. In every case the glycosuria appears to have been slight and transient. Bramwell expressly refers to "a distinct trace of sugar" in one case. I found, in one patient only, upon two successive days, 0·2 and 0·1 per cent. of glucose (confirmed by polarization, fermentation, and formation of osazones).[2] During treatment, even after sugar was given, none appeared in the urine. In Luxemburg's patient,

[1] Dennig (46) considers the sugar to have been galactose in his case. This case is often quoted without criticism, but the proof for the statement is not conclusive.

[2] In several of the cases there is no proof that the reducing body was sugar.

a girl of nineteen, the glycosuria remained as " a trace " during organotherapy extending over several months ; the treatment, however, was not very successful. In view of all the facts, it is not satisfactory to attribute the glycosuria present in these cases to the diseased thyroid. And the moderate appetite of such patients does not suggest that an overfilling and occasional emptying of the glycogen stores is likely to occur. It is possible that here a form of renal glycosuria has to be dealt with.

E.—THE THEORY OF THE ACTION OF THE THYROID GLAND.

1. *The Secretion Theory.*—This expresses the most common view held as to the action of the thyroid [Baumann, Roos, Oswald, and others (50)]. It supposes that the gland secretes, in the colloid material, an active substance, which passes into the circulation *via* the lymph-stream and exerts its influence upon the body generally. Whether this influence takes place through the central nervous system,[1] or whether there is a direct chemical action between the substance and the various organs of the body, can only be surmised. In the case of the action of the thyroid upon the heart alone has this action been proved to be independent of the brain and spinal cord [Cyon and others (51)].

It has often been assumed that when the normal thyroid secretion is absent metabolism is altered both qualitatively and quantitatively ; also that under these circumstances poisonous products—" toxines "—are formed which otherwise either do not appear at all, or appear, but are neutralized by the thyroid substance. In this sense the thyroid secretion is conceived of as a kind of " antitoxine " for " toxines " which originate in the healthy tissues. Attempts have recently been made to base a system of organo-therapy for cases of Graves' disease upon this assumption. Investigators have hoped to extract these " toxines " from myxœdematous animals, and have given the materials thus obtained to patients suffering from Graves' disease, in whom it is supposed that too much of the hypothetical " antitoxine " is present. But these efforts at isolating " toxines " from thyroidectomized animals have not yet been fraught with certain success [Formanek, Baldi, and others (53)].

Herzberger (54) speaks of the " antitoxine " of the thyroid gland as " thyreohaptin." This transference of Ehrlich's views and expressions from the sphere of immunity to that of internal secretions does not, however, lead us much further, for it deals only with speculation, and not with any results of experimental investigation.

2. *The Neutralization Theory* [Notkin, F. Blum (55)].—The secretion theory includes, as already mentioned, the notion of neutralization, but in this second theory, which is opposed to the first, the seat of neutraliza-

[1] Oswald (51) considers that this substance exerts a direct action upon the kidneys as well as upon metabolic processes generally. Investigations have been undertaken with the purpose of ascertaining if the destruction of albumin in the body is increased under the influence of thyroid feeding. Schryver (52) found that this did occur. But an increase of tissue destruction, as surmised by Oswald, would not of itself explain an increase in the total oxidation processes. Wells found that the addition of thyroid extract to liver pulp *in vitro* produced no increase in the autolytic action taking place (52).

tion is supposed to take place in the thyroid gland itself, and not in the rest of the body through the medium of a secretion. According to Blum, the thyroid takes up toxic substances which arise as the result of metabolic processes, and so clears the organism of these. The iodine of the thyroid secretion is supposed to combine with the poisons, and to neutralize them in the gland; the iodine then reunites with the albumin of the gland, and is thus retained in this situation so as to be ready for further neutralization. The iodine thus exerts its specific function only within the gland, and never leaves it. This author bases his views firstly upon finding that the lymph glands proper to the thyroid, and the resulting lymph itself, were free from iodine. But more accurate study of this point causes the alleged fact to lose much of its importance (Blum only examined 100 c.c. of lymph, and this was certainly not derived exclusively from the thyroid gland). The second point leading this author to his conclusions was his finding that the amount of iodine in the thyroid gland of dogs fed upon iodine-free food was comparatively high; he therefore argued that the iodine never left the gland. Apart from theoretical considerations, however, the experiments of Baumann and of Miwa and Stöltzner (56) are opposed to Blum's views. These observers found a very low iodine content under the conditions of Blum's experiment. But there are other objections to this author's views. The action of thyroid extract in myxœdema, congenital thyreo-aplasia, and cachexia strumipriva, where the gland is occasionally absent, is much against them, for here, at any rate, the action of the extract must be exerted outside the gland. Blum's answer to this objection, that the cure of myxœdema can only take place through an increase of oxidation processes, is contrary to all clinical experience. And even so, Blum admits that the increase of metabolism induced by thyroid extract is independent of the presence of thyroid tissue. It may further be argued against Blum's views that the iodine substance which possesses a specific action is not, according to Oswald and others, stored up in the cells of the gland, but is contained in the colloid; the "toxine" to be dealt with would therefore need first to diffuse into this colloid, and then to undergo a purely chemical process of neutralization without the medium of the cells of the gland.[1]

The Active Substance of the Thyroid Gland.

Only a short résumé of the most important facts can be given here. The iodine discovered by Baumann is only found in organic combination, more particularly in a protein molecule (57). This protein body, the iodine-containing thyreo-globulin of Oswald, only appears in the colloid, and not in the cells of the gland [Hutchison (57), Oswald]. But according to Kocher, goitres which are free from colloid occasionally contain iodine (57). The activity of this iodine substance is not affected by the action of pepsin, trypsin, weak alkalis, and strong acids. During its digestion iodine-containing albumoses are produced [Oswald], and these, according to Hutchison, exert a feeble action in myxœdema; and also

[1] For a more detailed criticism of Blum's views, see Kraus (55).

peptones, which Tambach found contained iodine, but Oswald found were free from it. Iodine-free peptones are certainly not active [Hutchison]. The specific action is still preserved by the small residue which is left after boiling the substance with hydrochloric acid—the thyro-iodin or iodo-thyrin of Baumann. This latter, varying as it does in actual iodine content, is certainly not a uniform body. But if, as appears to be the case judging by unanimous clinical and experimental results, this body possesses full activity,[1] it is nevertheless (according to Tambach) not the same body which operates in the organism; for it does not arise as the result of peptic or tryptic digestion, and therefore cannot be formed in the alimentary canal from the digestion of thyroid gland substance.

But we must admit that in the organism itself a more elaborate disintegration of the products of pancreatic digestion as well as of thyro-iodine, may well take place. These lower disintegration products may either themselves retain the full physiological activity of the thyroid, or they may regain it after further synthesis. According to Oswald the iodine is not contained in the tyrosin molecule. Mosse and Neuberg (59) have undertaken investigations which tend to show that the iodine of the iodized protein substance is contained in a phenol group.

It is only the iodine-containing products of the thyroid gland which are specifically active [Baumann, Roos, Hutchison, Oswald, and others]. Neither the iodine-free thyreoglobulin of Oswald, nor the nucleo-protein of Oswald, nor the extractives which contain Fraenkel's thryeo-antitoxin, nor the basic products isolated by Drechsel (62), are specifically active [Baumann, Roos, Hutchison, Magnus-Levy]. On the whole, it may be

[1] The physiological activity of any substance isolated from the thyroid gland may be tested in regard to the following points:

1. Its actions upon the pulse and upon the heart [Hellin, Cyon, and others]. Definite results are only obtained by the use of large doses of any active substance.
2. Its action upon nitrogen (and phosphorus) metabolism [E. Roos], and especially upon the gas exchanges [Magnus-Levy]. The evidence of loss of weight is of itself not reliable.
3. Its effect in bringing about diminution in the size of goitres [Emminghaus and Reinbach, Roos].
4. Its action in the myxœdema of man [Magnus-Levy, Leichtenstern, Kocher, and others].
5. Its life-saving influence upon thyroidectomized animals.

The result of this last investigation is not decisive so far as human pathology is concerned. According to Wormser and Stabel's careful experiments and clinical investigations (58) (contrary to other authors), no single substance isolated from the gland is capable of imitating the action of the gland itself in saving life in thyroidectomized animals. But in animal experiments a condition of acute tetany has to be dealt with, and this is said by Moussu, Vassale, and Generali [followed by A. Biedl and Chvostek (60), A. Pineles, and others] to depend, not upon the extirpation of the gland, but upon removal of the parathyroids or epithelial bodies. And the function of these bodies is very different from that of the thyroid gland (12a).

Considering the most important of the various bodies which have been isolated in the light of these tests, the activity of *thyreoglobulin* has been proved by its action in nitrogen metabolism [Oswald], upon the heart [Cyon and Oswald], and upon myxœdema [Magnus-Levy]; *thyro-iodine* has satisfied tests 1 to 4. If, as is the case according to some authors (61), this substance acts less powerfully than does the total thyroid gland, this is not a point of serious importance. As a matter of fact, we do not possess a practical standard for comparing these different substances; the standard of absolute iodine content is not wholly satisfactory. This difficulty is increased by the fact that the substances are not themselves uniform chemical compounds. Voit, who considers the iodine content of importance, found in his experiment that the amount of iodine in the less active iodo-thyrin was smaller than in his thyroid extract tabloids.

said that in feeding experiments those glands which are rich in iodine have, bulk for bulk, a better action than those less rich in iodine [Baumann, Roos, Oswald, and others]. But it is impossible to decide whether this turns upon a greater iodine content of the thyreoglobulin or upon a larger amount of thyreoglobulin having a constant iodine content. For it is impossible to separate the thyreoglobulin that contains iodine from the thyreoglobulin that is iodine-free [Oswald], and even the chemical uniformity of iodine-thyreoglobulin is a matter of doubt. By the exhibition of potassium iodide and organically combined iodine it is possible to raise the iodine content of the thyroid gland in the body [Baumann, Roos, Blum, Oswald]. With this rise in iodine, too, the activity of the gland substance increases. But treatment of the thyroid gland protein—or, at least, of the thyro-iodine—with iodine *in vitro* appears to destroy its special properties [Blum, Roos, Oswald, Hutchison]. Contrary to Blum's statements, other artificially iodine-treated protein substances possess no specific properties. Nor, according to Baumann, does Drechsel's "gorgonin," the iodine-containing body derived from coral. On the other hand, it is stated by Salomon (62A) that the substance "korpulin," said to be obtained from seaweed, increases the nitrogenous metabolism and the gas exchanges in man, and thus acts in a manner similar to thyroid substance.

Iodine taken internally as a salt has no action in myxœdema; it possesses no influence, either clinically or experimentally, upon metabolism [Magnus-Levy]. And in other diseases, and in healthy persons, it is without demonstrable metabolic effect. [For protein metabolism see Boekh and Cederkreutz; for O_2 and CO_2 see Magnus-Levy; for CO_2 see Bloch, Cederkreutz (63)].

Lastly, pituitary substance has no influence upon the gas exchanges, nor upon the clinical picture of myxœdema [Magnus-Levy; see Acromegaly]. The same may be said of ovarian substance [Hutchison (64)].

The Amount of Iodine in the Thyroid Gland.

According to its geographical derivation, the normal thyroid gland of man contains 0·3 to 0·9 milligramme of iodine per gramme of thyroid substance, or from 2 to 9 milligrammes of iodine in the whole gland (65). The thyroid glands of the fœtus and the new-born are free from iodine (65), as also are those of Zurich calves [Oswald]. Hen's eggs are free from organic iodine [Miwa and Stolzner] even when the hens have been fed with potassium iodine [Levene]. In children over one year old—that is, after a mixed diet has been commenced—iodine appears in the thyroid, but only in small amounts [Baumann, Jollin, Charrin, Fr. Weiss]. According to Oswald, the iodine content of the thyroid in children is not relatively, but only absolutely, less than in adults. A few investigations made upon the iodine content during old age showed a low figure [Baumann, Jollin]. During pregnancy the amount of iodine is said to diminish considerably [Monéry; Kocher found that the reduction might be to one-thirtieth of the normal]. According to Baumann, goitres usually contain

relatively less iodine than healthy thyroids, but according to Oswald, Fr. Weiss (65), Monéry (66), and A. Kocher (67), they often contain absolutely more, the amount rising to 50 or even to 100 milligrammes. Purely parenchymatous goitres are, on the other hand, entirely free from iodine [Oswald], or only contain very little [Th. Kocher (67)]. Amongst this latter class come the goitres of Graves' disease [Seligmann, Oswald, E. Gley]. Matthes found less than 0·002 milligramme per gramme, and Kocher estimated the amount as one-thirtieth that of normal glands (68).[1] Purely fibrous goitres are also free from iodine ; so, too, are any parts in a condition of cystic degeneration (66). Ewald (69) found an adeno-carcinoma of the thyroid to be free from iodine, but the metastatic deposits contained iodine. Oswald considers that the iodine content of goitres runs parallel, on the whole, with the amount of colloid present, but with marked colloidal degeneration the iodine is relatively diminished, or may even disappear.

The highest iodine content is found in herbivorous animals ; the omnivorous come next ; in carnivorous animals the iodine content is lowest, and may be absent altogether (70). Whereas iodine feeding leads to the appearance, and increase, of iodine in the thyroid of dogs, this is not the case, according to Anselm, in cats, in whose thyroids no iodine is found even after iodine feeding. [But this has lately been denied by Boeniger (70)].

Iodine in Other Organs.—At first it was stated by Baumann (71) that iodine was absent from most other situations in the body. More recently, however, it is said to have been demonstrated in several organs. But it is doubtful if all investigators have worked with the same degree of care as the discoverer of the thyroid gland iodine.

In any case, the iodine content of all the organs, with the possible exception of the suprarenal glands, is relatively much less than that of the thyroid. I find the following facts recorded (71) in this connection :

The Pituitary Body.—No iodine [Baumann, Rositzky, Paderi] ; some iodine [Ewald, Schnitzler (71)].

The Thymus.—Very little iodine [Baumann] ; no iodine [L. B. Mendel (71)].

The Muscles.—No iodine [Baumann, Treupel, Zülzer] ; a little iodine after iodine feeding [F. Blum (71)] ; a little iodine [Bourcet].

The Spleen.—Barrel found an amount of iodine in the large spleen of cattle which was absolutely as large as in the thyroid, but the relative amount was much smaller.

The Ovaries.—Barrel found some iodine in the ovaries of the pig.

The Parathyroids.—According to Mendel, the parathyroids of man contain absolutely and relatively more iodine than the thyroid. Chenu and Morel found iodine in these organs.

The Suprarenals.—Some iodine [Barrel].

The Hair.—Usually free from iodine, but the administration of iodine increases the amount considerably [Howald, Dreschsel (71)].

The Milk.—Iodine is present or absent according to the diet [Bourcet].

[1] A larger iodine content in some goitres of Graves' disease was caused by iodine taken as a drug.

Finally, Justus (71) was able to demonstrate that in man iodine was present in the liver, kidneys, and ovaries, but that the iodine content of the thyroid was always eight to ten times as high as of the organ next richest in this element. Boeniger has more recently arrived at similar results.

According to Nagel and Roos (72), *bromine* is not found in the thyroid, not even after bromide feeding. But Baldi reports a positive result in this respect, both as regards the thyroid and the pituitary glands [Paderi (72)].

Arsenic has been found by Gautier and Bertrand in the thyroid gland and in organs developed from the ectoderm, and Bertrand has confirmed this in deep-sea animals, in whom accidental contamination can be excluded. Gautier concludes that this element is excreted by the hair in man, and also, in the female, by the menstrual blood. The presence of arsenic in the thyroid is denied by German observers [Hödlmoser and others], but Bertrand's analytical technique appears to have been very thorough.

Some Critical Comments upon the Secretion Theory.

Although the writer accepts the secretion theory, and admits the doctrine of the specific value of the organically combined iodine, it is well to draw attention to some difficulties in connection with the theory.

One of the chief defects in the secretion theory is due to our inability to estimate the amount of iodine which is constantly being reformed in the thyroid and then entering the body; we are only able to measure the amount of iodine present in the gland at any given moment. Again, we know very little about the varying activities of different substances of unequal iodine content. It is not certain that every milligramme of this or that "substance" acts specifically in the organism; a portion may be stored up by its undergoing some indifferent chemical combination, or it may, to use Ehrlich's appropriate word, be "diverted." In this case, although in the strict chemical sense no actual destruction of the substance could take place, yet, biologically speaking, it would certainly be equivalent to a destruction: there would be an annihilation of its specific property. We are ignorant as to whether the active substance, after exerting its specific action, is regenerated (within or outside the thyroid gland), thus observing a continuous circulation similar to that proved to occur in the case of the bile acids. Some of these points, the enumeration of which does not exhaust the uncertainties attaching to the secretion theory, may perhaps be discussed somewhat more fully.

The presence or absence of iodine in the thyroid gland of carnivorous and of suckling animals depends upon whether or not their diet contains iodine. In order to establish the validity of the iodine secretion theory, the additional hypothesis must be added that but very small quantities of iodine (which their diet probably gives these animals) are necessary to the formation of the specific thyroid substance, by way of constant

transformation in the gland and subsequent excretion into the general circulation; for these minute quantities are certainly insufficient to admit of a storage of iodine substance. The conditions present in Graves' disease require a very different explanation. The goitres present in the disease are nearly always purely parenchymatous, are poor in colloid,[1] and usually also poor in iodine (*vide supra*). It is hence assumed that in Graves' disease the thyroid is unable to fix sufficiently well the iodine or iodine substance [Kocher].[2] But, on the other hand, it must be added that the gland nevertheless forms continually more iodine substance than does the normal organ. Were this not so, the daily excretion of the active substance could not, after the exhaustion proceeding in the gland, be greater than in health.[3] It is tempting to consider the amount of this normal secretion as being the smallest quantity which, in the cured myxœdematous patient, just suffices to prevent a recurrence of the disease—*i.e.*, a quantity equivalent to about 3 milligrammes of organic iodine. But it remains a question whether this added quantity of active substance acts as a whole (after synthesis or other transformation), or as a part, the other (and perhaps the bigger) having been previously used up or disintegrated. This conception furnishes one possible explanation why thyroid substance derived from the same source exerts such marked action in some persons, whilst in others larger quantities remain entirely inactive. It must again be urged that an arithmetical addition of iodine substance by ingestion to that already found in the body is quite a different procedure from that taking place naturally. On the other hand, it is not certain that all the secretion of the thyroid gland is utilized in the body for purposes known to us. It is quite possible that a portion of it is set aside for a different use, and therefore results in by-products which have, as yet, been lost sight of.

If, then, the purely quantitative relations of the thyroid secretion are almost totally unknown, and are much too complicated to allow of our following out a theory of "hyperthyreosis" in all its details, how much less does our knowledge of the qualitative deviations in thyroid function enable us to argue a theory of "dysthyreosis"? All that has

[1] Hämig assumes that in patients with colloid-containing goitres the colloid degeneration is of older date than the Graves' disease, the symptoms of which have been superadded. Such colloid goitres have been observed by Hämig, Oswald, Reinbach, and others (73A).

[2] Kocher, for this reason, speaks of Graves' disease as a condition of "hypothyrea"; this seems to us, in relation to the secretion theory, unwarrantable, and likely to lead to confusion. But if we understood this author's Munich lecture correctly, Kocher appears to be a follower of the doctrine of hyperthyreosis in Graves' disease. The goitre of Graves' disease certainly does not lack ability to store iodine in organic combination if given in sufficient amount in the diet. Baumann and Oswald (74) were able to demonstrate this fact.

[3] Otherwise it would be necessary to assume that the same quantity of the same "iodine substance" taken up by the body acts more powerfully in Graves' disease than in health. This possibility could be conceived of as occurring in different ways. The "iodine substance" most likely exerts its proper action chemically by the formation of a more or less stable compound; but we may imagine that (both in health and disease) the activity of the substance is not exhausted by the formation of one compound—*i.e.*, the specifically active substance might become liberated and act again several times; and perhaps in Graves' disease this action occurs more frequently than in health. True this and similar speculations are mere hypotheses, for whose possibility or probability we cannot vouch. But these speculations must be considered in examining the value, and in noting the gaps in the completeness of, the "iodine-secretion theory."

hitherto been adduced in favour of such a view is but speculation. Such an hypothesis affords as yet no points for analytical or experimental investigation, and therefore we can assign no value to it.

Kocher (75) has attempted to trace the fate of the iodine of healthy and goitrous persons by observing the excretion of iodine after the administration of 0·2 gramme of potassium iodide. In some goitrous subjects, as well as in one or two myxœdematous patients, Kocher found a higher retention of iodine than in health. On the other hand, other observations showed an actual loss of iodine by the body; in these cases the goitres diminished in size, with a diminution in relative and absolute iodine content. But the absolute quantities of iodine given off from the body, or retained in it, were much too large to refer them to the iodine changes going on in the thyroid gland—they sometimes amounted to 50 milligrammes daily. By means of these investigations certain valuable therapeutic hints may have been gained, but no satisfactory explanation of the dependence of certain pathological appearances upon changes in the iodine metabolism has been arrived at. The same remark may be applied to another of Kocher's results. This investigator found a certain antagonistic relation existing between the phosphorus and the iodine content of the thyroid gland, the one rising as the other falls. According to Kocher, an increase in metabolism of phosphorus causes, especially in Graves' disease, a marked increase in the iodine percentage in the gland—in one case the iodine rose from 0·008 milligramme to 1·02 milligrammes. With this increased capacity of the gland for iodine fixation the phosphorus content sank about 40 per cent.

LITERATURE.

1. Myxœdema.

1. *General Works.*—Ewald: Erkrankungen der Schilddrüse. Nothnagel's Handb. **1896.**—Buschan: Ueber Myxödem. **1896.**—Byrom Bramwell: Anæmia, etc. **1899.** (Myxœdema. P. 287.)—Heinsheimer: Entwick. und Stand der Schilddrüsenbehandlung. **1895.** Report on Myxœdema. T. Cl. S. **21.** Suppl. 1888.—Thorel: Path. der Schilddrüse. Er. P. **7.** 169 ff. 1902.—Scholz: Ueber Kretinismus. 1906. See also under Lit. Nr. 3.—See further on the Imporance of the Parathyroids and Epithelial Bodies.—Biedl: Innere Sekretion. W. K. **1903.** Okt.-Nov.—Pineles: Physiol. der Schilddrüse und Epithelkörperehen. G. M. C. **14.** 120 ff. 1904.—Kraus u. Kocher: Über die Pathol. der Schilddrüse. Discussion at the 24 K. i. M. (Münehen), **1906**; and B. M. J. 1906. Vol. i., p. 1261.

2. Magnus-Levy: (*a*) Untersuch. zur Schilddrüsenfrage. Z. M. **33.** 1897. P. 286.—(*b*) Ueber Myxödem. Ibid. **52.** 201 ff. 1904.—Andersson: Stoffwechsel bei Myxödem. Hygiea. **60.** 1898. Ma. **1899.** 427.

3. Ord and White: Urine in Myxœdema after Thyroid Gland. B. M. J. **1893.** 2. 216.—Vermehren: Stoffwech. naeh Behandl. mit Gland. thyr. D. m. W. **1893.** 1037.—Magnus-Levy: S. Nr. 2a.—Widal u. Javal: Ėehanges nutritifs chez un myxœdémateux. C. r. S. B. **54.** 495. Ma. **1902.** 734.—Andersson: Nr. 2.—Scholz: V. C. M. **1902.** 475; and Ueber den Stoffw. der Kretinen. Z. e. P. 2. 271. 1905.

4. Ernst Maier: Stoffwech. thyreoektomierter Kaninchen. Diss. Würzb., **1897.**—Baldoni: Ace. di Roma. **25.** 319. 1899. Ma. **1899.** 558.—L. Smith: Some Effects of Thyroideetomy in Animals. J. P. **16.** 378.—Michaelsen: Einfl. der Exstirpat. der Schilddrüse auf den Gasweehsel. Ar. P. M. **45.** 622. 1889.—Bloch: Nr. 24.

5. Dutto e Monaco: Stoffwech. bei Hunden nach Thyreoidektomie. Ar. i. B.

24. 196. 1895.—Roos: Ueber die Wirk. des Thyrojodins. Z. p. C. **22.** 18 1896. P. 58.—Ver Eecke: Corps thyreoide et échanges organiques. Ar. i. P. **4.** 1897. — Verstraeten: Cit. by Ver Eecke. — Gluzinski u. Lemberger: Entfernung der Schilddrüse und Stoffwechsel (poln.). Ma. **1899.** 492. — Formanek: Zur Kennt. der strumipriven Kachexie (böhmisch). Ma. **1896.** 555. —Ducceschi: Oxydationsvorgänge, etc., bei thyreoidektomierten Tieren. Ar. i. B. **26, 27.** Ma. **1897.** 488.

6. Mendel: D. m. W. **1893.** 25.—Zumbusch: Schilddrüsenbehandl. bei Myxödem. D. Zt. **2.** 444. 1895. — Napier: L. **9.** 2. 805. 1893. — Ferranini: Ueber einen von der Schilddrüse unabhängigen Fall von Mitralinfantilismus. Ar. P. N. **33.** 296; Bi. C. **1905.** 746.—Ord and White: Nr. 3.—Vermehren: Nr. 3. — Treupel: Stoffw. bei einem mit Jodothyrin behandelten Myxödem. Mü. m. W. **1896.** 885.—Magnus-Levy: Nr. 2a.—Andersson: Nr. 2.—Widal u. Javal: Nr. 3.—Calabresi: Congr. soc. méd. int. **1899.** (Ma. **1899.** 474.)

7. Ewald u. Breisacher: Fall von Myxödem. B. k. W. **1895.** 25, 55.—Houghardy u. Langstein: Stoffwech. bei infant. Myxödem. Ja. K. **61.** 634. 1905.—W. Scholz: Nr. 3.—Bernheim-Karrer: Atypical Myxœdema. Ja. K. 1906. Bd. 14.

8. Ord and White: Nr. 3.—Widal u. Javal: Nr. 3.—Haushalter u. Guérin: Stoffwechselstör. bei infant. Myxödem. R. M. E. 1902. 211.—Houghardy u. Langstein: Nr. 7.—Magnus-Levy: Nr. 2a.—W. Scholz: Nr. 3.—Mosler: Cit. by Buschan: Nr. 1a. P. 69.

9. Byrom Bramwell: l.c., No. 1.—Pfeiffer u. Scholz: Nr. 14.—Bleibtreu u. Wendelstedt: Nr. 15.—Andersson u. Bergmann: Nr. 14.—Jaquet u. Svenson: Nr. 15.

10. Byrom Bramwell: Nr. 1. P. 311.—Guérin, cit. by Buschan: Nr. 1. P. 69.—Hofmeister: Folgezustände der Schilddrüsenexstirpation. D. m. W. **1896.** 345.—Dieballa u. Illyes: Stoffwechselunters. an Brightikern unter Schilddrüseneinwirk. E. A. **39.** 272. 1897.

11. Buschan: Nr. 1. P. 66.—Schneider: Zusammensetz. des Blutes, etc. Diss. Dorpat, 1891, and C. P. **1891.** 363.—Formanek u. Hascovec: Funktion der Schilddrüse. **1896.** Pp. 32, 52.—Albertoni u. Tizzoni, cit. by Lanquiritio: Acc. di Siena. 1893. (Ma. **1894.** 422.)—Lévy: Blood of Dogs after Removal of the Thyroid. J. P. and B. **1898.** 316.—Masoin: Oxyhämoglobin im Blut Myxödematöser. C. r. S. B. **47.** 73, 214; Ma. **1895.** 210.—Lebreton: Du sang dans le myxœdème. Mercredi méd. **1895.** 29.—Kraepelin u. Lézius, P. Ehrlich, cit. by Gottstein: Versuche zur Heilung der Tetanie. D. Zt. Nervenheilk. **6.** 177.

12. Zésas, Bardeleben, Albertoni u. Tizzoni, Gley, Zanda: See G. Gottstein, Nr. 11.—Fano: Rapporti funzionali del corpo tiroideo. Ar. i. M. **1893,** and Ma. **1894.** 436.—Hutchison: J. P. **23.** 178. 1899.

12a. See Magnus-Levy: Organther., in Karewski's ärztl. Bibliothek. **1906.**

13. Stevenson, cit. by Halliburton: (*a*) T. Cl. S. **21.** Supp. P. 48.— (*b*) Mucin in Myxœdema. J. P. and B. **1892.** 6.—Harley: Pathol. of Myxœdema. M.-C. T. **49.** 197. 1884.—West, cit. by Buschan: Nr. 1. Pp. 71, 72.—Juergens: Myxödem. St. P. **1889.** 447.—Hunn and Prudden: On Myxœdema. A. J. M. S. **96.** 153. 1888.—Lebreton: Nr. 11.—Buzdygan: Zwei Fälle von Myxödem. W. k. W. **1891.** 570.—Bramwell: Nr. 1. P. 336.—Bourneville: Mucine dans la peau d'un myxœdémateaux. Ar. n. **16.** 121. 1903.

2. Action of Thyroid Substances on Non-Myxœdematous Persons.

14. Vermehren: Nr. 3. — Dennig: Stoffw. bei Schilddrüsenther. Mü. m. W. **1895.** 389, 464.—Buerger: Stoffwech. des gesunden Menschen bei Schilddrüsenfütterung. Diss. Halle, 1895.—Scholz: Schilddrüsenbehandl. und Stoffw. des Menschen insbes. bei M. Basedowii. C. i. M. **1895.** 1041.—Ver Eecke: Nr. 5.—Richter: Eiweisszerfall nach Schilddrüsenfütterung. C. i. M. **1896.** Jan.—Gluzinsky u. Lemberger: Einfl. der Schilddrüsenbehandl. auf den Stoffwechsel. Ibid. **18.** 89. 1897.—Andersson u. Bergmann: Einfl. der Schilddrüsenbehandl. beim gesunden Menschen. Sk. Ar. P. **8.** 326. 1898.— Pfeiffer u. Scholz: Stoffw. bei Paralysis agitans und im Senium. D. Ar. M. **63.** 369 ff. 1899.

15. *Obesity.*—Zinn: Stoffwechselvers. mit Schilddrüsentabletten bei Fettsucht.

B. k. W. **1897.** 577.—Bleibtreu u. Wendelstedt: Stoffwechselvers bei Schilddrüsenfütterung. D. m. W. **1895.** 347.—Grawitz: Thyrojodin und Stoffw. bei Fettsucht. Mü. m. W. **1896.** 312.—Magnus-Levy: Nr. 2a. P. 304 ff.—Jaquet u. Svenson: Stoffw. fettsüchtiger Individuen. Z. M. **41.** 375. 1900. P. 394 ff.—Schiödte: Thyreoidea bei Entfettungskuren. Ar. V. **5.** 1. 1899.

16. Georgiewsky: Wirk. der Schilddrüsenpräp. auf den tier. Organismus. Z. M. **33.** 153. 1897.

17. Dinkler: Stoffw. bei Gebrauch von Schilddrüsensubstanz. Mü. m. W. **1896.** 512.—Irsai, Vas u. Gara: Thyreoideapräparate bei Strumakranken. D. m. W. **1896.** 439.—Senator: Osteomal. und Organther. B. k. W. **1897.** 109.—Pfeiffer u. Scholz: Nr. 14.—Schiff: Beeinflus. des Stoffwech. durch Hypophysis und Thyreoideapräparate. Z. M. **32.** 284. 1897.—David: Schilddrüsenpräp. und Stickstoffaussch. im Harn. Z. H. **17.** 439. 1896.—Treupel: Stoffwechselunter. bei einem mit Thyrojodin behandelten Fall. Mü. m. W. **1896.** 117.

18. Richter: Nr. 14.—Voit: Stoffwechselunter. am Hund mit frischer Schilddrüse und Jodothyrin. Z. B. **35.** 116. 1897.—Andersson u. Bergmann: Nr. 14.—Andersson: Einfl. der Schilddrüsenbehandl. bei Myxödem. Sk. Ar. P. **14.** 224. 1903.—Magnus-Levy: Nr. 2a.—Andersson: Nr. 2.—Bleibtreu u. Wendelstedt: Nr. 15.—Schiödte: Nr. 15.—Schöndorff: Einfl. der Schilddrüse auf den Stoffw. Ar. P. M. **67.** 395. 1897.

19. Richter: Nr. 14.—Dieballa: Nr. 10.—Mayer: Einfl. von Nuklien- und Thyreoideafütterung auf die Harnsäureaussch. D. m. W. **1896.** 186.—David: Nr. 17.—Dennig: Nr. 14.—Pfeiffer u. Scholz: Nr. 14.—Irsai, etc.: Nr. 17.

20. Roos: Nr. 5.—Ver Eecke: Nr. 5.—Irsai: Nr. 17.—Scholz: Nr. 14.—Andersson u. Bergmann: Nr. 14.—Pfeiffer u. Scholz: Nr. 14.—Buerger: Nr. 14.—Senator: Nr. 17.—Richter: Nr. 14.—Scholz: Nr. 14.—Jaquet u. Svenson: Nr. 15.—A. Schiff: Nr. 17.—Georgiewsky: Nr. 16.

21. See the authors under 14 and 15.—Tikanadse: Thyreoidin und Ausnutz. des Nahrungsfettes beim gesunden Menschen. Diss. Petersb., 1897; and Ma. **1897.** 486.

22. Magnus-Levy: Gaswech. bei Thyreoida, etc. B. k. W. **1895.** Nr. 30; Magnus-Levy: Nr. 2a.—Thiele u. Nehring: Respirat. Gaswech. bei. Thyreoideapräparaten. Z. M. **30.** 41. 1896.—Stüve: Respirat. Gaswech. bei Schilddrüsenfütterung, Morb. Basedowii, etc. Festschr. Städt. Krankenh. **1896.**—Jaquet u. Svenson: Nr. 15.—Andersson u. Bergmann: Nr. 14.—Speck: Abkühlung, Lichtreizung und Stoffwechselbeschleunigung. Z. M. **43.** 377. 1901.

23. Bramwell: Nr. 1.—Notthafft: Artefizieller akuter thyreogener M. Basedowii. C. i. M. **1898.** 353 ff.—Becker: D. m. W. **1895.** Nr. 37.—Jaenike: Thyreoideapräp. bei einigen seltenen Krankheitsfällen. C. i. M. **1901.**

24. Bleibtreu u. Wendelstedt: Nr. 15.—Voit: Nr. 18.—Bloch: Einfl. von Jod, Thyrojodin und Thyraden auf den Stoffw. Diss. Würzb., **1896.**—Schöndorff: Nr. 18.

3. Graves' Disease.

25. *General Works.*—Möbius: Die Basedow's Krankheit, Nothnagel's Handb. **1896.**—Buschan: Die Basedow's Krankheit. **1896.**—Mannheim: Der Morbus Gravesii. **1894.**—Bramwell: Anæmia, etc. **1899.**—Minnich: Das Kropfherz. **1904.**

26. Müller: Zur Kennt. der Basedow's Krankheit.. D. Ar. M. **51.** 335. 1893.

27. Magnus-Levy: Nrs. 22 and 2a.—Stüve: Nr. 22.—Salomon: Gaswechselunters. bei M. Basedowii. B. k. W. **1904.** Nr. 24.

28. Speck: Nr. 22.

29. Hirschlaff: Zur Path. und Klin. des M. Basedowii. Z. M. **36.** 200. 1899.

30. Lustig: Stoffw. bei der Basedow's Krankheit. Diss. Würzb., **1890.**—Müller: Nr. 26.—Tourette et Cathélineau, cit. by Möbius: Nr. 25. P. 50.—Matthes: Zum Stoffw. bei M. Basedowii. V. c. M. **1897.** 232.—Scholz: Nr. 14.—Kocher: Ueber M. Basedowii. G. M. C. **9.** 1902. P. 141.

31. Buschan : Nr. 25.—Möbius : Nr. 25. P. 48.—Hirschlaff : Nr. 29.
32. May : Stoffw. im Fieber. Z. B. **30.** 1. 1893.
33. Daddi e Marchetti : Ricambio materiale in un caso di morbo die Flaiani. Cl. M. **1904.** Bi. C. **1904.** 752.
34. Schreiber u. Waldvogel : Zur Kenntnis der Harnsäureaussch. E. A. **42.** 69. 1899.—David : Nr. 17.—Kocher : Nr. 30. P. 141.
35. Kocher : Nr. 30. P. 140.—Bramwell : Nr. 25. P. 400.
36. Chvostek : Aliment. Glykosurie bei M. Basedowii. W. k. W. **1892.** Nr. 18.
37. Boinet et Silber, cit. by Möbius : Nr. 25. P. 50.
38. Schreiber u. Waldvogel : Nr. 34.—Dreschfeld, cit. by Bramwell, Nr. 25. P. 400.
39. Hannemann : Glykosurie und Diab. bei M. Basedowii. Diss. Berl., 1895. —Schmidt : Diab. mell. bei Basedow-Krankheit. Diss. Würzb., 1892.
40. Kocher : Nr. 30. P. 144.
41. Roos : Nr. 5.
42. Irsai, Vas u. Gara : Nr. 17.—Dinkler : Nr. 17.
42a. Beebe : New Serum for Exophthalmic Goître. J. A. M. A. 1906. Nr. 7. —Rogers : Specific Sera in Goître. J. A. M. A. 1906. Nr. 7.

4. Thyroid and Carbohydrate Metabolism.

43. Hannemann : Nr. 39. — Naunyn : Diab. mellitus. **1898.** P. 77. — Schreiber u. Waldvogel : Nr. 34.—Salomon : Nr. 27.—Grawitz : M. Basedowii mit Diab. mell. F. M. **1897.** 849.—von Noorden : Die Zuckerkrankheit. **1901.** P. 49.—Kocher : Nr. 30. P. 140.—Budde, cit. by Hannemann : Nr. 39.
44. Ludwig u. Kraus : W. k. W. **1891.** Nrs. 46, 48.—Chvostek : Nr. 36. —Strauss : Neurogene und thyreogene Glykosurie. D. m. W. **1897.** 275.— Zülzer, cit. by Naunyn : Nr. 43.—Friedheim : Nebenwirk. der Thyreoidea. Festschr. B. Schmidt. **1896.**—Naunyn : Nr. 43. P. 77 ff.—Magnus-Levy : Nr. 2a. P. 308 ff.—Kocher : Nr. 30.—von Noorden : Schilddrüsenther. bei Fettleibigen und M. Basedow. Z. p. A. **1896.** Nr. 1.—Diénot : Glycosurie dans la mal. de Basedow. Thèse de Lyon. **1899.**
44a. Porges : Zur Wirk. und Nachwirk. des Schilddrüsengiftes. B. k. W. **1900.** 300.
45. Ewald : Nr. 7.—Lorand : Rapp. du diabète avec l'acromeg., etc. P. m. **1903.** Nr. 75.
46. James : B. M. J. **1894.**—Notthafft : Nr. 23.—Dennig : Nr. 14.— von Noorden : Nr. 44.—Friedheim : Nr. 44.—Béclère : Myxœdème guéri, etc. Mercredi méd. **1894.** 511.
47. Mawin : Die Glykosurie erzeugende Wirk. der Thyreoidea. B. k. W. **1897.** 512.—Strauss : Nr. 44.—von Noorden : Nr. 44.—Bettmann : Einfl. der Schilddrüsenbehandl. auf den Kohlenhydratstoffw. B. k. W. **1897.** 518.—Grawitz : Nr. 43.
48. Hirschl : Jb. Psych. u. Neurol. **1902.** Cit. by Knöpflmacher : Aliment. Glykosurie und Myxödem. W. k. W. **1904.** 244.
49. Campbell, cit. by Buschan (1) : Myxödem. P. 69.—Juergens : Nr. 13. —Bramwell : Nr. 25. P. 311.—Magnus-Levy : Nr. 2b. P. 206.—Luxenburg : N. C. **1903.** 448.

5. Theoretical.

50. See Thorel : Nr. 1, and Biedl : Nr. 1.—For the Theory of Secretion, see Baumann, Roos, Oswald : Nr. 57 ff.
51. Cyon u. Oswald : Physiol. Wirk. einiger Schilddrüsenprodukte. Ar. P. M. **83.** 199. 1901.—Oswald : Nr. 57.
52. Schryver : The Influence of the Thyroid on Autolysis. J. P. **32.** 159. **1895.** Bi. C. **1905.** 662.—Wells : A. J. P. **11.** Nr. 4. 1904. Bi. C. **1904.**
53. Formanek : Nr. 5.—Baldi : Ar. i. B. **31.** 1899. (Ma. **1899.** 473.)
54. Herzberger : Bi. C. **1903.** 193.
55. Notkin : Ar. p. A. **144.** Suppl., 246. 1896.—Blum : (*a*) Halogenstoffwech., etc. Mü. m. W. **1898.** 231 ; (*b*) Ueber synthet. dargestellte Spezifika.

XV. K. i. M. **1897.** 226; (*c*) Jodwirkung der Schilddrüse. Z. p. C. **26.** 160. 1898; (*d*) Jodsubstanz der Schilddrüse. Ar. P. M. **77.** 70. 1899; (*e*) Schilddrüse als entgiftendes Organ. Ar. P. A. **158.** 495. 1899.

56. Baumann: Nr. 57c. — Miwa u. Stöltzner: Ist Jod ein notwendiger Bestandteil jeder normalen Schilddrüse? Ja. K. **45.** 87. 1897.

57. Baumann u. Roos: Jod im Tierkörper. Z. p. C. (*a*) **21.** 319; (*b*) **21.** 481. 1895; (*c*) **22.** 1. 1896.—Tambach: Chem. des Jods in der Schilddrüse. Z. B. **36.** 549. 1898. — Blum: Nr. 55a.—Oswald: (*a*) Eiweisskörper der Schilddrüse. Z. p. C. **27.** 14. 1899; (*b*) Chem. und Physiol. der Schilddrüse. Ar. P. M. **79.** 450. 1900; (*c*) Thyreoglobulin. Z. p. C. **32.** 121. 1901. (*d*) Thyreoglobulin. Be. P. P. **2.** 545. 1902; (*e*) Chemie u. Physiol. des Kropfes. Ar. p. A. **169.** 444. 1902; (*f*) Sammelreferat. Bi. C. **1903.** 249.—Roos: (*a*) Schilddrüse und Stoffwechsel. Z. p. C. **21.** 19. 1895; (*b*) Wirk. des Thyrojodins. Z. p. C. **22.** 18. 1896; (*c*) Jodothyrin. Z. p. C. **25.** 1, 242. 1898; (*d*) Schilddrüse. Z. p. C. **28.** 40. 1899; (*e*) Wirksame Stoffe der Schilddrüse. Mü. m. W. **1896.** 539.—Hutchison: Beitr. zur Schilddrüsenfrage. C. m. W. **1896.** Nr. 13; J. P. **20.** 474, and **23.** 178. 1899.—Kocher: Nr. 67.

58. Wormser: Exper. Beitr. zur Schilddrüsenfrage. Ar. P. M. **67.** 505. 1897. (Literature.)—Stabel: Jodothyrin, etc., an thyro-ektomierten Hunden. B. k. W. **1897.** 721.

59. Mosse u. Neuberg: Physiol. Abbau des Jodalbumins. Z. p. C. **37.** 427. 1903.

60. Biedl: Nr. 1.—Chvostek: Zur Aetiol. der Tetanie. W. k. W. **1905.** 969.

61. Gluzinsky u. Lemberger: Nr. 14.—Schiff: Nr. 17.—Bloch: Nr. 24.—Voit: Nr. 18.—Kocher: Über Schilddrüse. 23. K. i. M. **1906.**

62. Fraenkel: W. k. W. **1895.** Nr. 48; and W. m. B. **1896.** Nr. 13.—Drechsel: Wirksame Substanz der Schilddrüse. C. P. **9.** 24.

62a. Salomon: Korpulin. C. S. **2.** 205. 1901.

63. Boekh: Zersetz. des Eiweisses unter dem Einfluss von Hg und J. Z. B. **5.** 393. 1869.—Cedercreutz: Beitr. zur Kennt. des N-Wechsels bei Syphilis, Einwirk. therap. Hg- und J-Gaben. **1902.** Magnus-Levy: Nr. 2 (*a*).—Bloch: Nr. 24.

64. Hutchison: Nr. 57.

65. Baumann: Nr. 57.—Oswald: Jodgeh. der Schilddrüsen. Z. p. C. **23.** 265. 1897, and Nr. 57.—Weiss: Jodgeh. von Schilddrüsen in Schlesien. Mü. m. W. **1897.** 6.—Charrin et Bourcet: Jodgeh. der Gland. thyr. C. r. S. B. **52.** 339. (Ma.)—Mendel: Jod in Thymus und Schilddrüse. A. J. P. **3.** 235. —Miwa u. Stöltzner: Nr. 56.—Levene: Ma. **1901.** 586.—Jollin: Jodgeh. schwedischer Kröpfe. N. m. A. Festband, **1897.** (Ma.)—Kocher: Nr. 67.

66. Monéry: Fonction jodée de la glande thyroide. Jo. P. **19.** 288; and Bi. C. **1904.** 652.

67. Kocher: Zweites Tausend Krokfexstirpationen. Ar. k. C. **64.** 454. 1901.—Kocher: Ausscheid. des Jods bei Strumen. G. M. C. **14.** 360. 1905.

68. Seligmann, cit. by Kocher: Nr. 67. P. 249.—Oswald: Nr. 57c.—Matthes: Nr. 30.—Kocher: Nr. 67.—Gley: C. r. S. B. **53.** 399.

69. Ewald: Jodgeh. des Adenocarcinoms der Schilddrüse. W. k. W. **1896.** 186.

70. Baumann: Nr. 57c.—Roos: Über die Schilddrüse. Z. p. C. **28.** 40. 1899.—Oswald: Nr. 57c.—Anselm: Jodaufspeicherung nach Jodfütterung. Diss. Würzb., **1900.**—Kraus: Nr. 1.

71. Baumann: Nr. 57c. — Rositzky: Jodgeh. von Schilddrüsen in Steiermark. W. k. W. **1897.** 823.—Paderi: Vorkommen von Brom, etc. Ma. **1899.** 463.—Ewald u. Schnitzler: W. k. W. **1896.** 657.—Baumann: Ueber Thyrojodin. Mü. m. W. **1896.** 309.—Mendel: Nr. 65.—Treupel: Nr. 6. —Zülzer: V. C. M. **1897.** 240. Discussion.—Blum: Nr. 55.—Barrel: Jod in Ovarien. Pharmaz. Ztg. **42.** 130. (Ma. **1897.** 492.)—Chenu u. Morel: C. r. S. B. **56.** 681. 1904; Bi. C. **1904.** 685.—Howald: Jod in Haaren. Z. p. C. **23.** 209. 1897.—Drechsel: Jod im menschl. Organismus. C. P. **9.** 24. 1896.—Bourcet: C. r. S. B. **132.** 1364. (Ma. **1901.** 142.)—Justus: Physiol. Jodgeh. der Zelle. Ar. p. A. **176.** 1904. (Bi. C. **3.** 559.)—Boeniger, cit. by Fr. Kraus: S. Nr. 1.

72. Nagel u. Roos: Exper. Beeinflussbarkeit des Jodgehalts der Schilddrüse.

Eng. A. **1902.** Suppl. 267.—Baldi: Brom in der menschl. Schilddrüse. C. P. **12.** 679. 1898.—Paderi: Nr. 71.

73. Gautier: C. r. S. B. **129.** 929. Fonction menstruelle, etc. Rôle de l'arsénic. C. r. S. B. **131.** 361. Ma. **1900.** 737. Z. p. C. **36.** 391. 1902. —Bertrand: An. P. **16.** 553. **17.** 1. 1903. — Hödlmoser: Arsen, etc. Z. p. C. **33.** 328. 1901.

73a. Hämig: Anatom. Untersuch. über M. Basedowii. Diss. Zürich, 1897.—Oswald: Nr. 57c. and 57d.—Reinbach: Oper. Ther. beim M. Basedowii. G. M. C. **6.** 189. 1900.—*Cf.* also Kocher: Nr. 67. P. 215 ff., 229, and Thorel: Nr. 1.

74. Baumann: Nr. 57c.—Oswald: Nr. 57d.

75. Kocher: Aussch. des Jods bei Strumen. G. M. C. **14.** 360. 1905.

II.—ACROMEGALY.

Unlike the results of investigations upon metabolism in diseases of the thyroid gland, the results of similar observations made in acromegaly serve to elucidate but few of the clinical features of the disease, and help little in the study of its pathogeny.

Neither pathological anatomy, nor experimental pathology, nor investigations into the chemical processes taking place in the disease, suffice to establish with certainty the dependence of acromegaly upon changes occurring in the pituitary body. And if, as most observers believe, this dependence exists, it none the less remains wholly undetermined whether we have to deal with an increase or with a decrease in the functions of this organ.

In some patients the tissue changes during rest, so far as the figures for oxygen and carbon dioxide are concerned, may be increased [Magnus-Levy, 270 c.c. O_2 in a patient of 52 kilogrammes—*i.e.*, 5·19 c.c. O_2 per kilogramme; Salomon in two cases associated with diabetes]. The occasional occurrence of bulimia as a symptom in acromegalic patients who are not glycosuric also points in the same direction. In other cases, however, which have been studied, the gas exchanges were certainly not increased [two cases by H. Salomon]. If acromegaly be associated with myxœdema, the exchanges may even be diminished [Magnus-Levy].

Several authors have noted a small retention of nitrogen [A. Schiff in a case associated with myxœdema; Moraczewski, Franchini, Edsall and Miller], and have explained it by growth of tissues. But this growth usually takes place very slowly, and the explanation is not satisfactory in the case reported by Moraczewski, where a retention of nitrogen persisting for several weeks was associated with a loss of weight of 3 kilogrammes.

Retention of phosphorus, calcium, and chlorides has been observed by Moraczewski (for several weeks a daily storage of 1 gramme of phosphorus), and also by Edsall and Miller. From the greater retention of phosporus as compared with calcium, American authors have supposed a deposition of phosphorus in the bones and soft parts. Franchini found that nitrogen, lime and magnesia were retained at the same time that phosphorus and chlorine were lost.

Urea was found in Moraczewski's case to be relatively increased (80 to 95 per cent. of the total nitrogen), ammonia increased (3 to 4 per cent.), and uric acid about normal (1 to 2 per cent.). Franchini found that the uric acid excretion varied from 0·6 to 1·8 grammes, and that the sulphur derivatives were excreted in normal amounts.

That there are relations existing between the hypophysis cerebri and other glands of the hæmopoietic system—however mysterious these relations may be—is certain. And these relations are seen best in the case of the thyroid. Some of the symptoms of Graves' disease or of myxœdema frequently appear in the course of acromegaly. Of special interest in connection with metabolism is the sweating which is frequently present, the increased oxidation proved to occur in some cases, and the oft-noted occurrence of mild or severe grades of diabetes. All these manifestations suggest analogies with Graves' disease. The glycosuria which occurs with acromegaly is etiologically rather obscure. Loeb and Naunyn conceive of a cerebral form of diabetes, while Hausemann and others describe a pancreatic form. The diabetes we are now considering has no clinical distinctions nor metabolic features different from those of ordinary diabetes.

Feeding with increased quantities of pituitary extract produces no rise in the gaseous exchanges of healthy persons [Salomon], and little or no rise in patients suffering from acromegaly [Magnus-Levy, Salomon], or from myxœdema [Magnus-Levy]. The excretion of nitrogen remains practically unaltered in healthy persons under these conditions [A. Schiff]; in acromegaly it rises more or less [Schiff, Franchini, Moraczewski]. In Schiff's cases the phosphorus excretion was also somewhat increased, but this was not observed in Moraczewski's cases. Acromegalic patients, according to both these authors, respond to thyroid treatment in much the same way as healthy persons.

There is no doubt that the influence of the pituitary body upon metabolism is much less marked than that of the thyroid. And when, in an acromegalic patient, an increase of metabolic changes is found, this should be referred to associated disease of the thyroid rather than disease of the hypophysis cerebri [Magnus-Levy]. It should also be noted that in practice the use of pituitary extract in the treatment of acromegaly has less effect than the use of thyroid preparations [M. Sternberg].

LITERATURE.

Sternberg: Akromegalie. Nothnagel's Handbuch. 1897.

Pineles: Beziehungen der Akromegalie zum Myxödem, etc. Vo. s. V. 242. 1899. (Literature.)

Schmidt: Die Knochenerkrank. bei Akromegalie. Er. P. 5. 914. 1900.

Magnus-Levy: (*a*) Zur Schilddrüsenfrage. Z. M. 33. 298. 1897. P. 298. (*b*) Der respirat. Gasw. in Krankh. Z. M. 1906.

Salomon: Gaswech. bei M. Basedowii u. Akromegalie. B. k. W. 1904. Nr. 24.

Schiff: Beeinfluss. des Stoffwech. durch Hypophysis, etc. Z. M. 32. Suppl. 289. 1897.

Moraczewski: Stoffwech. bei Akromegalie, etc. Z. M. 43. 336. 1901.

Franchini: Ricambio materiale in acromegalia. Boll. scienze med. Bologna. Ann. 75. Bi. C. 1905. 522.

Edsall and Miller: Chem. pathol. of Acromegaly. U. Pa. Vol. xvi., 1903, p. 143.

Naunyn: Diabetes mellitus. Nothnagel's Handb. 1899. 80. Literature on Sugar Excretion in Acromegalie. See also Moraczewski, H. Salomon, Launois, and Rey: C. r. S. B. 55. 382. 1903, etc.

III.—ADDISON'S DISEASE.

The suprarenal glands have been proved by experimental pathology to be necessary for life; removal of them causes death in a few days. Apart from a few good results obtained in the treatment of Addison's disease, however, experimental therapeutics have as yet found no adequate substitute for the missing organs. The production of adrenalin by the medullary substance of the suprarenal—the presence of which body in the blood of the gland may be accepted as proved—is not the only function of the organ; Biedl and others regard the cortex as of still greater importance, supposing that it possesses the function of neutralizing various noxious principles arising in the body.

No observations have yet been undertaken with a view of explaining the immediate relations existing between the suprarenals and human metabolism. It is true that Blum looks upon bronzed diabetes as a form of suprarenal diabetes, but this is not the case. In this connection should be mentioned the property of raising the blood-pressure possessed by adrenalin [Oliver and Schaefer], the experimental relations existing between the glands and arteriosclerosis, and the glycosuria which occurs after the administration of adrenalin [Blum]. One other matter deserves comment: Neusser denies the immediate dependence of pathological pigmentation upon disease of the suprarenals. But feeding with suprarenal gland has caused the spots present in a series of cases to become lighter, or even to disappear for longer or shorter periods; this observation has thus made the hitherto doubtful dependence quite certain.

It will suffice merely to indicate the chief results which have followed the few metabolic investigations that have been made.

In surveying these metabolic researches the impression is obtained that Addison's disease patients—usually persons in a reduced state of nutrition—can easily hold their ground upon a normal, or even upon a rather spare, diet [Kolisch and Pichler, Martin Jacoby, M. Pickardt, Martin Kaufmann, Marchetti and Stefanelli, Allaria and Varannini]. They generally gain in nitrogen, weight, and richness of ash upon a full diet [Senator, Vollbracht]. The "metabolic flash-point" is therefore not raised. Food assimilation in the intestine is normal, only being disturbed if diarrhœa is present [Jacoby], but bad utilization of fat has been noted by Pickardt. According to Senator, Kaufmann, and Allaria, the administration of suprarenal extract hinders absorption, but Pickardt arrived at the opposite conclusion. Again, the observations of Senator, Pickardt and Allaria showed a prejudicial effect of the substance upon the nitrogen balance, whilst those of Kaufmann showed a favourable one. Just as upon the clinical picture, so upon metabolism, the extract

acts variably in different cases ; but its effect is much weaker than that of the thyroid gland.

With regard to the excretion of urea, uric acid, and ammonia, normal percentages were found by Neusser's pupils, Kolisch and Freund ; but low values for uric acid and creatinin are noted by Leva (upon what diet ?). Vollbracht records an instance of lime and magnesia retention running parallel with a nitrogen retention, the body losing phosphorus at the same time.

Several of the older references to the presence of taurocholic and hippuric acids, neurin and " fatty acids " in the urine of patients with Addison's disease have partly lost their value and partly require confirmation.

Mosse found that extracts of organs from cases of Addison's disease were toxic when injected into animals. And after extirpation of the suprarenals similar results were obtained by the use of the organs from the affected animals. But from these bald facts to the isolation of the " toxines " of normal metabolism, supposed to be neutralized by the suprarenal gland, is a far cry.

During certain intoxications, such as those of phosphorus-poisoning and diphtheria, during uræmia and some acute infections, as in Addison's disease, adrenalin may disappear from the suprarenal glands [Luksch]. Further investigations along the line of this discovery are certainly indicated, and may lead to important results.

LITERATURE.

General Works.—Neusser : Erkrankungen der Nebennieren. Nothnagel's Handb. **1897.**—Chvostek : Pathol. Physiol. der Nebenniere. Er. P. **9.** II. 243. 1905.—Fürth : Über die chem. Natur des Adrenalin, etc. Bi. C. **2.** 1. 1904.—See also Elliot on Adrenalin. J. P. **31.** 1905.

Oliver and Schäfer : Physiol. Action of Glandular Extracts. J. P. **18.** 277. 1896.

Cybulski, cited by Szymonowicz : Ar. P. M. **64.** 97. 1897.

Ehrmann : Wertbestim. des Adrenalin. E. A. **53.** 97. 1905.

Jossué : C. r. S. B. **55.** 1374. 1905.—Erb : Arterienerkrank. nach Adrenalin. E. A. **53.** 173. 1905.

Blum : Ueber Nebennierendiab. D. Ar. M. **71.** 146. 1901.

Kolisch u. Pichler : Fall von Mb. Addisonii mit Stoffwechselunters. C. i. M. **14.** 249. 1893.

Pickardt : Beeinfluss. des Stoffw. bei Mb. Addisonii durch Nebennierensubst. B. k. W. **1898.** 727.

Jacoby : Ueber Durchfälle. Ch. An. **23.** 286. 1898.

Kaufmann : Stoffwechselbeob. bei einem mit Nebennierentabletten behandelten Fall von Mb. Addisonii. C. S. **2.** 173. 1901.

Marchetti u. Stefanelli : Riv. crit. di clin. med. **1901.** Ma. **1902.** 671.

Allaria u. Varannini, cit. by Chvostek (l. c.). P. 286.

Senator : Stoffwechselvers. bei Addison. Krankheit. Ch.-An. **22.** 235. 1897.

Vollbracht : Fall von M. Addisonii, etc. W. k. W. **1899.** 737.

Kolisch, Freund, cit. by Neusser : P. 57.

Leva : Zur Lehre vom M. Addisonii. Ar. p. A. **125.** 35. 1891.

Mosse : Zur Lehre von der Autointox. bei M. Addisonii. F. M. **15.** 818. 1897.

Luksch : Funktionsstör. der Nebenniere bei Allegemeinerkrank. W. k. W. **1905.** Nr. 14.

Fraenkel : Zur Ther. des M. Addisonii. Diss. Breslau, 1900. (20 cases.)

Magnus-Levy : Organther., in Karewski's Moderner ärztl. Bibliothek. **1906.**

CHAPTER XI

THE RARER DISTURBANCES OF PROTEIN METABOLISM

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As with carbohydrates and fats, so with protein substances and their cleavage products, no more than traces pass into the urine in the normal individual. Under pathological conditions, it is true, small amounts of these substances are occasionally met with in the urine, as in acute yellow atrophy of the liver, phosphorus-poisoning, and in metabolic disturbances such as diabetes and gout, and in leuchæmia and pneumonia, etc.

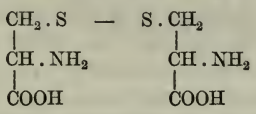
Anomalies, however, which are in their essence dependent on a chemically closely circumscribed disturbance of protein metabolism, are rare ; only three of this express kind are known—cystinuria, diaminuria, and alkaptonuria.

I.—CYSTINURIA.

1. General.

The first detailed researches on the excretion of cystin which took account of its chemical nature are those of Baumann and von Udránzki (1). In this anomaly the cystin appears in the urine partly as sediment and partly in solution. Baumann and his fellow-workers (2) thought they had already cleared up the constitution of cystin. Cystin was first observed in 1810 by Wollaston (3) in a urinary calculus, then more closely examined by Thaulow (4), as well as by Külz and Mauthner (4). But the investigation of cystin entered on a new phase when von Mörner (6) recognised it as a constituent of almost all protein substances, and thus made the possibility of an accurate examination of it a matter independent of its rare occurrence in calculi and in the urine of the cystinuric.

Simultaneously and independently of one another, C. Neuberg (7) and E. Friedmann (8) showed that the old views as to the constitution of cystin were incorrect, and that the formula



must be ascribed to it.

The first indications of the presence of isomeric cystins in the protein molecule are due to K. A. H. von Mörner (9). Neuberg and Mayer (10) came to the conclusion that in many cystin calculi there is an isomer which differs from the typical protein cystin.[1] Nevertheless there doubtless occur cystin calculi of ordinary cystin [C. H. Rothera (11), McKim Marriott, and C. G. L. Wolf (12)], and the question of isomerism is not yet finally settled [E. Fischer and U. Suzuki (13)].

2. The Behaviour of Cystin in Normal Metabolism.

Like the products of hydrolysis of all true protein substances, cystin is an amino-acid ; but it occupies a special position in so far as it contains an important mineral substance, namely, sulphur. Sulphur is present in the proteins in two forms, one firmly combined (oxidized), and the other, the predominating amount, in an easily separable, not oxidized, form. The quantity of the latter is almost completely covered by the quantity of cystin which can be prepared from the protein substances. Many circumstances point to the conclusion that the sulphur present in the so-called oxidized form has nothing to do with the protein molecule proper, but that in this case there is at most an ester-like combination of the protein molecule with sulphuric acid.[2] Accordingly the sulphur which enters, in true organic binding, into the metabolic changes is for the most part present in the cystin group, and it is clear, therefore, that cystin plays an essential part in the sulphur metabolism.

The relationships so expressed become evident in the ratio between the cystin and the intermediate and final sulphur product.[3]

Sulphur is present in urine in four different kinds of combination : as sulphate, as ethereal sulphate, as neutral sulphur, and in many cases as a basic compound. All these forms are transformation products of cystin.

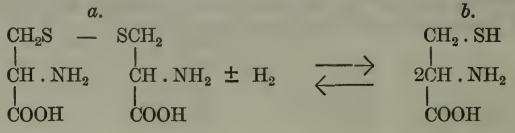
When cystin is given it does not pass as such into the urine. In the dog, Goldmann (14), after feeding with 2·02 grammes cystein[4] hydrochloride, observed that two-thirds of its sulphur was excreted as sulphate and one-third as so-called neutral sulphur. A considerable part of the

[1] The chief part of the cystin which arises from the hydrolysis of protein crystallizes n six-sided tables ; the cystin of cystin urine almost always shows this same crystalline form. A needle-shaped form of cystin is also obtained from horn as well as from many cystin calculi (see Literature, 9 and 10).

[2] On this view the binding of the oxidized sulphur would correspond in some measure to the joining up of phosphoric acid through the prosthetic group in the nucleo-proteins.

[3] Whether cystin, as may be conjectured, also stands in relation to the thiocyanic acid (SHCN) metabolism has not yet been investigated.

[4] All sorts of reducing agents transform cystin (*a*) with extraordinary ease into cystein (*b*) :



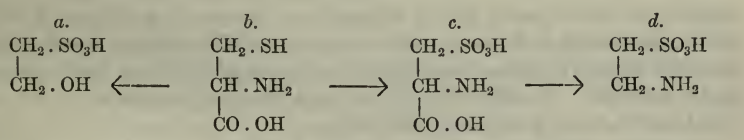
Cystein (= α-amino-β-thiopropionic acid), on the other hand, is very easily oxidized again—*e.g.*, even in air—to cystin, the corresponding disulphide.

latter consists, according to Wohlgemuth (15) of hyposulphites, the source of which is therefore likewise cystin. In fact, cystin also passes easily on oxidation in alkaline solution *extra corpus* into hyposulphurous acid [L. Spiegel (16), C. Neuberg and P. Mayer (10)]. According to the researches of L. Blum (17) on rabbits and dogs, and also of A. Loewy and C. Neuberg (18) and of C. H. Rothera (11) on men, the oxidative transformation of cystin sulphur is complete.

Of the commoner volatile organic sulphur compounds, among others, methyl mercaptan (CH_3SH) is probably present in the intestinal gases, in addition to H_2S. Abel (19) found it possible to obtain one such compound by treating dog's urine with alkalis; he considered it to be ethyl sulphide $(C_2H_5)_2S$. Now there is obtained from cystin by heating it under pressure a mixture of gases smelling like ethyl sulphide and mercaptan [Neuberg and Mayer (20)], and J. Wohlgemuth (15) was able to show that sulphuretted hydrogen and methyl mercaptan, as well as ethyl sulphide, arise by the bacterial decomposition of cystin. Finally, the antecedent substance from which the ethyl sulphide of dog's urine is set free by action of alkali is, according to Neuberg and Grosser (21), a salt of a basic sulphur compound—diethylmethylsulphinium hydroxide, $(C_2H_5)_2S\langle^{CH_3}_{OH}$. Presumably its formation is to be explained in such wise that ethyl sulphide is produced owing to putrefactive changes in the intestine from a part of the sulphur group of the protein substances, and is resorbed and undergoes physiological "methylation." Perhaps, too, the methylated compound arises directly in the organs.

Free cystin had repeatedly been found in organic tissues before its discovery as a protein fraction—namely, by Scherer (22) in a man's liver, by E. Drechsel (23) in the same organ in the horse and dolphin, and by Cloetta (24) in an ox's kidney. The investigation of the constitution of cystin has alone prepared the way for the recognition of its relations to organ metabolism proper, while those occasional discoveries were unable to give any impulse in this direction.

C. Neuberg (7) had found that cystein (*b*), by oxidation, passes into isethionic acid (*a*), and it had been shown by E. Friedmann (8) that cystein (*b*), by oxidation, can be transformed first into cysteic acid (*c*), and subsequently by splitting off of CO_2 into taurine (*d*):



The relationships to taurine and to isethionic acid, which stand to each other in the relation of amino- to oxy-acid, then completely cleared up the important part played by cystin in the metabolism of bile.

G. von Bergmann (25), by means of experiments on a dog with a biliary fistula, adduced the proof that the biliary constituent taurine does arise

from cystin when cholalic acid is at its disposal for union with it. On feeding herbivora with cystin, J. Wohlgemuth (15) observed an increase of the biliary sulphur, even without the addition of cholalic acid.

Whether the synthesis of taurocholic acid succeeds with taurine as such, or whether the cystin and biliary acids first yield an intermediate product which is subsequently oxidized to taurocholic acid, remains as yet undecided. L. Blum (17) found that liver pulp in presence of defibrinated blood is without action on cystin. After injecting the latter into the mesenteric vein, Blum also noticed in the bile a body which contained sulphur that could easily be split off—the so-called cystin sulphur —and at the same time gave the cholic acid reaction. It may be that this result speaks in favour of the second of the above assumptions.

3. The Chronic Excretion of Cystin.

The limit of oxidation for cystin, just as for other amino-acids, is quite high; this follows consistently from the experiments of Wohlgemuth, Rothera, and Blum, already mentioned. The last-named authors found, indeed, that even on inundating the intestine to the limit of toxicity there resulted no excretion of cystin in the urine. No alimentary cystinuria which could possibly be compared to an alimentary glycosuria has ever been described.

But cases of true chronic cystinuria are relatively numerous. In view of their essential similarity, there is no occasion to describe them one by one. The clinical description of these cases—if there can be said to be one at all—has been thoroughly done by Loebisch and W. Ebstein (26).

The quantity of cystin excreted in cystinuria varies from quantities barely recognisable to as much as 1·5 grammes per day. Apart from the excretion of cystin, the composition of the urine, which, it may be noted, very often shows a weak alkaline reaction even when quite fresh, may be otherwise completely normal [Loewy and Neuberg (18)]; but there are also cases known in which the urea was below the normal [E. Bödtker (27)], others in which the ammonia was diminished [C. Alsberg and O. Folin (28)], while, conversely, McKim Marriott and C. G. L. Wolf (29) observed that it was increased. Similar variations have been alleged of the excretion of creatinin and uric acid. The frequently alleged increase of the neutral sulphur at the expense of the inorganic sulphates is a matter of uncertainty, inasmuch as from the statements in the literature it is not evident that the alleged increase is not due to an error arising from cystin remaining in solution. E. Bödtker (27) has also observed uncombined sulphuretted hydrogen in solution in the urine.

Cystinuric cases permit of a natural division into two categories: those which are accompanied by excretion of diamines, and those which are not. But as, apparently, just as many cases are known with as without simultaneous diaminuria, and diaminuria also appears without any cystinuria whatever, diaminuria must be considered as a separate anomaly (see the following section).

4. Etiology of Cystinuria.

Cystinuria is a metabolic disturbance which may make its appearance at any time of life in males or females, perhaps somewhat oftener in the former. Thompson found it in a man eighty-one years old, Bödtker (27) in a boy of eleven years, and Abderhalden (30) in a child of one and three-quarter years. In the latter case, which was examined post-mortem at the Basle Pathological Institute, there was a notable cystin diathesis, which, according to Kaufmann, is unique of its kind, for the internal organs (liver, kidneys) were in part thickly covered with cystin deposits which were visible to the naked eye.

The relatively frequent hereditary character of cystinuria is remarkable. It has been repeatedly observed through several generations, and in children of the same parents ; this disposition of families was quite early recognised [F. Toel (31), Marcet, Pfeiffer (32), and Cohn (33), Abderhalden (30)].

Cystinuria has often been alleged to have relationships to other diseases—thus to articular rheumatism [Ebstein (26)] ; to gout, to cirrhosis of the liver and acholia [Morawsky]. But cases presenting not the slightest clinical peculiarity have been observed still oftener, and as, moreover, the causal connection between those affections and this metabolic anomaly has not yet been established, cystinuria must be considered as a metabolic disturbance *sui generis*.

5. The Relations of Cystinuria to Protein Metabolism.

Prior to the time when cystin was found to be a product of the disintegration of protein substances it had been conjectured, on the ground of its content in sulphur and nitrogen, that it might be a product of the intermediate protein metabolism. The explanation which von Udránzki and Baumann gave of its excretion corresponds in principle to that which is familiar to-day for the appearance of conjugation products of glycuronic acid and of glycocoll in urine. Like the latter, it should normally be further oxidized, and only in presence of definite bodies should it be intercepted. These authors considered these binding substances to be the previously mentioned diamines, especially putrescine and cadaverine, which they had found in the urine and in the fæces of a cystinuric patient [*cf.* also (35)]. The formation of the diamines was supposed to be brought about by specific bacteria in the digestive tract by an extraordinary chronic intestinal mycosis. The resorbed part of the cadaverine and putrescine was supposed to protect the cystin from combustion, just as benzoic acid does glycocoll, by entering into a loose combination which decomposes again after passing through the kidneys.

Serious difficulties, however, have opposed themselves to this interpretation of cystinuria. First, numerous cases have been described without simultaneous diaminuria, and, conversely, diaminuria occurs

in malaria, and in the conditions brought about by the cholera vibriones and the Finckler-Prior bacillus, without cystinuria having ever set in, any more than it does when diamines themselves are administered [Baumann and Udránzki (1)].

Further, in an hereditary constitutional anomaly, an intestinal mycosis of such a chronic character is in the highest degree improbable, and we surely ought to be able to contend against it with intestinal disinfectants; but neither B. Mester (36) with salol, nor Bödtker (27) with resorcin, could perceive any influence, and just as fruitless were the labours of other authors in this direction.

Besides, cases are known[1]—for example, Bödtker's (27)—in which the diaminuria vanished while the cystinuria persisted.

By a long series of experiments it has been ascertained that cystinuria is largely independent of diet (36, 37). Alsberg and Folin's (28) patient, who excreted cystin uninterruptedly after a period of thirteen days on a diet practically free from nitrogen, is another example of this fact. On the ground of the behaviour of crystalline products from the hydrolysis of protein in the organism of their patient, Loewy and Neuberg (18) have lately arrived at a widened conception of cystinuria.

While monamino-acids like leucin, tyrosin, aspartic acid, and cystin, when taken by the mouth, normally vanish as such absolutely, and are transformed into CO_2, H_2O, NH_3, and oxygen compounds of sulphur, these amino-acids reappeared in the urine of their cystinuric patient practically unchanged.

The diamino-acids behave similarly in cystinuria, but their fate is a little different. While in a normal man [W. H. Thompson (38)] they also are transformed into urea, in a cystinuric individual they are not burned off, but are transformed into diamines [Loewy and Neuberg]. The cystinuria of Loewy and Neuberg's patient was accompanied neither by diaminuria nor by the excretion of other amino- or diamino-acids: after administration of lysin there appeared in the urine cadaverine (pentamethylene-diamine); after an intake of arginin[2] the urine contained putrescine (tetramethylene-diamine). Unchanged diamino-acids do not pass in demonstrable amount into the urine; and the fact that after feeding with lysin (I.) cadaverine (II.) appeared, and after feeding with the diamino-valerianic acid (III.), which is the acid derived from arginin,[3] putrescine (IV.) appeared, excludes every other interpretation

[1] The case recorded by Garrod and Hurtley is one of these (see Garrod and Schölberg, *Lancet*, 1901, ii., p. 526, and *Journal of Physiology*, vol. xxxiv., p. 220, 1906).

[2] Five grammes of arginin carbonate were administered by Garrod and Hurtley in their case (*loc. cit.*), but no trace of putrescine could be detected in the urine, either by benzoylation or by the phenyl isocyanate method. This patient had excreted putrescine five years previously.

[3] Arginin is α-amino-δ-guanidine-valerianic acid:

$$H_2N\,.\,C(:NH)\,.\,NH{-}CH_2{-}(CH_2)_2{-}CH\,.\,NH_2{-}COOH,$$

a urea derivative of α-δ-diamino-valerianic acid. By means of an enzyme, arginase, discovered by Kossel and Dakin (39), which occurs abundantly in nearly all organs, arginin is decomposed with fixation of the elements of water into urea and diamino-valerianic acid:

$$H_2N\,.\,C(:NH){-}NH{-}CH_2{-}(CH_2)_2{-}CH\,.\,NH_2{-}COOH + H_2O = H_2N\,.\,CO\,.\,NH_2 + H_2N\,.\,CH_2{-}(CH_2)_2{-}CH.NH_2{-}COOH.$$

than that of a descent of the diamines from the corresponding diamino-acids.

I.	$CH_2NH_2—(CH_2)_3—CHNH_2—COOH$	Lysin.
II.	$CH_2NH_2—(CH_2)_3—CH_2NH_2$	Cadaverin.
III.	$CH_2NH_2—(CH_2)_2—CHNH_2—COOH$	Diamino-valerianic acid.
IV.	$CH_2NH_2—(CH_2)_2—CH_2NH_2$	Putrescine.

We have to deal with an example of the fermentative splitting-off of CO_2, several cases of which are already known. Thus A. Ellinger (40) was actually able to transform those diamino-acids by means of the bacteria of putrefaction into diamines, and the like transformation has been effected by Neuberg (41) by purely chemical methods.

Cystinuria thus presents itself as a disturbance of protein metabolism, and especially of the amino-acid metabolism. Of the end-products of protein hydrolysis which arise in his organism, the cystinuric cannot avail himself in the normal way of the cystin, and in part excretes it; the remaining products of protein hydrolysis undergo their ordinary fate. But if free monomolecular α-amino-acids appear in places which are at present not well known, or if they occur there even in unusual amount, then, unlike the normal individual, the cystinuric is unable to burn them, and they leave the organism unchanged just as cystin itself does. The basic diamino-acids behave in practically the same way, except that the CO_2 group is split off from them, and we arrive at diaminuria.

It is obvious that all cases of cystinuria need not show this distinctly marked character of a pronounced disturbance of amino-acid metabolism; it is rather probable that there are here—just as in diabetes—different degrees of the anomaly. Just as little as every glycosuria is accompanied by an excretion of acetone bodies, so little does diaminuria exist along with every cystinuria; and just as in diabetes the tolerance for other carbohydrates oscillates, so in cystinuria there exist distinctions in respect of the fate of other protein fractions.

These relationships, hitherto scarcely noticed, are important because they explain the differences which exist in the character of individual cases of cystinuria.[1]

1. Simon (42) established tolerance for tyrosin;[2] Alsberg (28) found that administered cystin (!), as well as aspartic acid, were completely burned; but their method was not wholly convincing. The examples of this class obviously constitute the smallest degree of metabolic disturbance.

2. The second category is represented by those cases which exhibit the character of the anomaly as described by Loewy and Neuberg. Left

[1] Three modifications are suggested by Garrod and Hurtley (*J. P.*, vol. xxxiv., p. 219, 1906): "It would appear, from what has gone before, that as regards any individual proteid fraction cystinurics fall into three main groups, comprising respectively those who habitually excrete the fraction in question either unaltered or, in the case of the diamino-acids, slightly changed; those who excrete it only when taken, as such, by the mouth; and those who do not excrete it under any circumstances."

[2] Five grammes of tyrosin were administered by Garrod and Hurtley to their patient: a small quantity of a substance melting at 253° C. was obtained. This may have been a tyrosin derivative. It was not obtained on any other occasion than after the administration of tyrosin.

to themselves, these cases excrete cystin only; but the inherent weakness of the oxidizing powers of the cystinuric patient for amino-acids appears on feeding him with isolated protein fractions.

3. In other cases—the third type—the disturbance in the intermediate protein metabolism appears to have progressed so far that, besides cystin, other amino-acids are spontaneously excreted, as tyrosin has been found in cystin urine[1] by Conti and Moreigne (43), and leucin, as well as tyrosin and small quantities of other amino-acids, by Abderhalden and Schittenhelm (44). Quite recently Garrod and Hurtley (34) observed a case in which the cystin was accompanied by a substance apparently closely related to tryptophane. The examples of cystinuria with simultaneous excretion of diamines appear as a special sub-group, in which the metabolic disturbance effects more of the protein molecule than the basic sulphur-containing complex.

The way in which the degree of the metabolic disturbance existing in cystinuria varies from case to case manifests itself as well in the very different quantities of cystin which are excreted as in the duration of this anomaly. There are examples in which cystinuria has been observed for twenty years, and to persist undiminished after this period [Loewy and Neuberg's case]; others in which an acute attack has come on and soon (after some months) passed away again [Bödtker's single case]; finally, others in which, after persisting for a year, it has slowly died away. In a similar case (not yet published) Loewy and Neuberg were able to reproduce the cystinuria in a slight degree after administration of large quantities of cystin, and at the same time to establish that the tolerance for administered tyrosin was also diminished.

Through its characterization as a disturbance of amino-acid metabolism cystinuria, which was formerly regarded more as a curiosity, now acquires a certain importance in the question of the fate of foodstuffs in the alimentary canal. If we observe that with some cystinurics monomolecular, free amino-acids, given *per vias naturales*, are, contrary to the normal, not burnt, but excreted unchanged or excreted as diamines after simply losing CO_2, then it is not evident why these individuals should not constantly excrete along with cystin, the remaining simple crystalline fractions of the protein molecule, if these, as is often assumed, appear in considerable quantity in the intestine. It must certainly make a difference if these products are formed gradually and physiologically, or if they suddenly inundate the intestine, or if they are present alone or with other protein fractions at the right place and in the proportions favourable for the rebuilding of protein.

The fact that, as a rule, tolerance for cystin alone is diminished may be connected with peculiarities of resorption as yet unknown, or even with a special, perhaps a loose, kind of binding of the sulphur group in the protein molecule; at any rate, cystin belongs to those fractions which are very early resolved from the protein molecule by the tryptic ferments of the intestine.

[1] Piccini and Conti, *Lo Sperimentale*, 1891, vol. xlv., p. 350; Moreigne, *Arch. de Méd. exp. et d'Anat. path.*, 1899, vol. xi., p. 254; Percival, *Archivio Italiano di Clinica Med.*, 1902, vol. xli., p. 50.

In view of the relations of cystin to taurin and to the formation of bile, Simon and Campbell (45) have suggested a disturbance of taurocholic acid synthesis (perhaps as a result of enzyme action) of such a kind that, in consequence of failure to utilize cystin, cystinuria makes its appearance. The attempts made by these authors to bring about the disappearance of a cystinuric condition by administration of bile acids have, however, had no result.

6. Experimental Cystinuria.

Baumann and Goldmann (46) recorded that traces of a cystin-like substance occur in normal dog's urine; the amount of this substance is said to be increased in phosphorus-poisoning. If in the last case the substance really is cystin, its formation is to be ascribed to the autolytic reduction of the tissue protein, which takes place in the phosphorus intoxication [Jacoby]. For cystin can be formed from protein substances not merely by acid hydrolysis and by the digestive enzymes, but also by the destructive action of intracellular ferments, and thus small quantities of cystin might be able, like leucin, tyrosin, and diamino-acids, to pass over into the urine.

Naturally, only a limited excretion of a sulphur-containing protein derivative is attainable by phosphorus-poisoning, but an artificial formation and excretion of cystin derivatives, which may be called in a certain sense an experimental cystinuria, can be arrived at in quite another way.

Jaffé (47), and Baumann and Preusse (48), found simultaneously in 1879 that the halogen substitution products of aromatic hydrocarbons, especially chloro-, bromo-, and iodo-benzene, and corresponding naphthalene derivatives, underwent a peculiar transformation in the organism which led to the formation of a highly complicated conjugated glycuronic acid (47, 48). The latter decomposed easily into glycuronic acid and the substance coupled with it, which in the cases mentioned is itself still a substance of complex structure, being at the same time a transformation product of the halogen derivative introduced and a derivative of cystin; these compounds are called mercapturic acids.

Their formation is to be interpreted as follows. For example, when bromobenzene (*a*) is introduced, it enters into a synthesis with cystin (*b*), and there is formed bromophenyl cystein (*c*); further, the latter unites in the organism with the acetyl group—the residue of acetic acid—to form the particular bromophenyl-mercapturic acid (*d*), which then unites in a manner not well known with glycuronic acid, and in this form passes into the urine.

a.	*b.*	*c.*	*d.*
C_6H_5Br	$CH_2 . SH$ $\vert$ $CH . NH_2$ $\vert$ $CO . OH$	$CH_2 . S . C_6H_4Br$ $\vert$ $CH . NH_2$ $\vert$ $CO . OH$	$CH_2 . S . C_6H_4Br$ $\vert$ $CH . NH . COCH_3$ $\vert$ $CO . OH.$

The different steps in this synthesis have been disclosed by the artificial breaking down of the mercapturic acids and their building up from cystin [Weiss (49), Friedmann (50)].

The formation of mercapturic acids may be compared with that of the conjugate glycocoll compounds hippuric acid and thiophenuric acid—

$$\begin{array}{l} CH_2 \cdot NH \cdot OC \cdot C_4H_3S \\ | \\ CO \cdot OH. \end{array}$$

In both instances the administration of a suitable binding substance is followed by the excretion, among the final products, of considerable quantities of a substance which under normal conditions is only scantily present or altogether absent. In this way the formation of the substance in question as an intermediate product of metabolism is proven.

According to Mester (36), the human organism is not adapted to perform this mercapturic acid synthesis; it is only consummated in the organism of the dog and of the rabbit. It fails even in birds [Bongers (51)].

It is to be remarked that after the administration of mercapturic acid producing substances the urine is strongly lævorotatory; the normal distribution of the sulphur in its various forms is, quite apart from the sulphur in the cystin, much disturbed [McKim Marriott and Wolf (52)], as if the administration of such compounds is by no means a matter of indifference to the organism.

7. Course and Therapeutics of Cystinuria.

As a rule cystinuria exhibits no clinical phenomena, and its existence has repeatedly been discovered accidentally; but occasionally it gives rise to gravel and stone formation, which may be followed by bladder and kidney troubles.

Apart from this, the character of this metabolic anomaly proper must be designated as quite innocuous, a view consonant with the frequent gradual cessation of cystinuria without any treatment.

Considering how largely cystinuria is independent of diet, and that it has so far been found impossible to actively influence it medicinally [Simon and Campbell (45)], therapeutic attempts must be limited to obviating those symptoms which may possibly be brought about by sedimentation of the sparingly soluble cystin. For this purpose several alkaline saline waters and sodium bicarbonate have been proposed, because cystin is easily soluble in alkali. Whether such a therapeutic treatment will prove effectual must remain a matter of doubt, when it is considered that fresh cystin urine is almost always alkaline.

8. Diagnosis of Cystinuria.

The recognition of cystinuria can, as soon as there is a sediment, be based on the complete combustibility of the precipitate obtained by recrystallizing the sediment from hot ammonia and on its microscopic appearance. Cystin usually forms typical six-cornered plates. If the

cystin is dissolved in the urine, it can frequently be made to separate, in the course of twelve hours, by acidifying slightly with acetic acid, if necessary, after previous concentration by evaporation. Cystin urine gives, like pure cystin, a heavy lead sulphide precipitate on warming with an alkaline lead solution (lead acetate and NaOH), a reaction which is yielded, though feebly, by almost every normal urine. A part of the cystin, however, always remains dissolved in the urine, and can be isolated by transforming it into sparingly soluble compounds [by means of benzoyl chloride (1, 46), mercuric acetate (20), phenyl isocyanate (10, 53), β-naphthalene sulphochloride (30), and α-naphthylcyanate (54)].

LITERATURE.

1. Baumann u. Udránzki: Diaminen bei Cystinurie. Z. p. C. **13.** 583. 1889; and Z. p. C. **15.** 77. 1891.
2. Baumann: B. C. G. **15.** 1734. 1882.—Suter: Die Bindung des Schwefels im Eiweiss. Z. p. C. **20.** 564. 1895.—Brenzinger: Cystin und Cysteins. Z. p. C. **16.** 552.
3. Wolleston: P. T. 1810. 223.
4. Thaulow: Annal. d. Chem. **27.** 197.
5. Külz: Zur Kenntnis des Cystins. Z. B. **20.** 1.—Mauthner: Zur Kenntnis des Cystins. B. C. G. **17.** 293. 1884.
6. Mörner: Zur Kenntnis der Bindung des Schwefels in den Proteïnstoffen. Z. p. C. **34.** 207. 1902.
7. Neuberg: Ueber Cysteïn. B. C. G. **35.** 3161. 1902.
8. Friedmann: Physiol. Beziehungen der schwefelhalt. Eiweissabkömmlinge. Be. P. P. **3.** 1 1902.
9. Mörner: Z. p. C. **34.** 295. 1902.—Zur Kenntnis der Spaltungsprod. des Cysteïns. Ibid. **42.** 363. 1904.
10. Neuberg u. Mayer: Ueber Cysteïn. Ibid. **44.** 472. 1905.
11. Rothera: Exper. on Cystein and its Relation to Sulphur Metab. J. P. **32.** 175. 1905.
12. Marriott and Wolf: The Composition of Cystin Calculi. M. M. J. **1906.** March.
13. Fischer u. Suzuki: Zur Kenntnis des Cystins. Z. p. C. **45.** 405. 1905.
14. Goldmann: Ueber das Schicksal des Cysteïns und die Entsteh. der Schwefelsäure im Tierkörper. Ibid. **9.** 269. 1885.
15. Wohlgemuth: Ueber die Herkunft der schwefelhalt. Stoffwechselprod. im tier. Organismus. Ibid. **40.** 81; and **43.** 469. 1904.
16. Spiegel: Beitr. zur Kenntnis des Schwefelstoffw. beim Menschen. Ar. p. A. **166.** 364. 1901.
17. Blum: Ueber das Schicksal des Cystins im Tierkörper. Be. P. P. **5.** 1. 1904.
18. Loewy u. Neuberg: Ueber Cystinurie. Z. p. C. **43.** 338. 1904.
19. Abel: Ueber das Vorkom. von Aethylsulfid im Hundeharn, etc. Ibid. **20.** 253. 1894.
20. Neuberg u. Mayer: Ueber d-, l- und r-Proteïncystin. Ibid. **44.** 498. 1905.
21. Neuberg u. Grosser: Eine neue schwefelhalt. Substanz aus dem Hundeharn. C. P. **19.** 316. 1905.
22. Scherer: Jahresb. ü. d. Fortschr. der Chem. 1857.
23. Drechsel: Beitr. zur Kenntnis des Stoffw. D. A. **1894.** 243.
24. Cloetta: Annal. d. Chem. **99.** 289. 1856.
25. von Bergmann: Die Ueberführ. von Cystin in Taurin im tier. Organismus. Be. P. P. **4.** 192. 1904.
26. Ebstein: Ein paar neue Fälle von Cystinurie. D. Ar. M. **23.** 138. 1878.
27. Bödtker: Beitr. zur Kenntnis der Cystinurie. Z. p. C. **45.** 393. 1905.

28. Alsberg and Folin: Protein Metabolism in Cystinuria. A. J. P. **14.** 54. 1905.
29. Marriott and Wolf: Cystinuria. A. J. M. S. **1906.** Feb.
30. Abderhalden: Familiäre Cystindiathese. Z. p. C. **38.** 557. 1903.
31. Toel: An. c. P. **96.** 247. 1885.
32. Pfeiffer: 4 Fälle von Cystinurie bei 4 Geschwistern. Ma. **1894.** 632.
33. Cohn: Ueber familiäre Cystinurie. B. k. W. **1899.** 503.
34. Garrod and Hurtley: On Cystinuria. J. P. **34.** 217. 1906.
35. Brieger u. Stadthagen: Ueber Cystinurie. B. k. W. **1889.** 344.
36. Mester: Cystinurie. Z. p. C. **14.** 109.
37. Leo: Ueber Cystinurie. Z. M. **16.** 325. 1889.
38. Thompson: The Physiolog. Effects of Peptone and Allied Products. J. P. **32.** 137. 1905.
39. Kossel u. Dakin: Ueber die Arginase. Z. p. C. **41.** 321. 1904.
40. Ellinger: Bildung von Putreszin aus Ornithin. B. C. G. **31.** 3183. 1899; Z. p. C. **29.** 334. 1900.
41. Neuberg: Eine neue Synthese der Diamine. Z. p. C. **45.** 110. 1905.
42. Simon: Ueber Fütterungsvers. mit Monoaminosäuren bei Cystinurie. Ibid. **45.** 357. 1905.
43. Conti u. Moreigne, cited by Simon: A. J. M. S. **119.** 48. 1900.
44. Abderhalden u. Schittenhelm: Ausscheid. von Leuzin und Tyrosin in einem Fall von Cystinurie. Z. p. C. **45.** 468. 1905.
45. Simon u. Campbell: Ueber Fütterungsvers. mit Cholalsäure bei Cystinurie. Be. P. P. **5.** 401. 1904.
46. Goldmann u. Baumann: Zur Kennt. der schwefelhalt. Verbindungen des Harns. Z. p. C. **12.** 254. 1888.
47. Jaffé: B. C. G. **12.** 1093. 1879.
48. Baumann u. Preusse: Zur Kennt. der Oxydat. und Synthesen im Tierkörper. Z. p. C. **3.** 156. 1879; and **5.** 309. 1881.
49. Weiss: Ueber die Anhydroester der *a*-Aminosäuren und eine Synthese der Merkaptursäuren. Ibid. **20.** 407. 1895.
50. Friedmann: Physiol. Beziehungen der schwefelhalt. Eiweissabkömmlinge. Be. P. P. **4.** 486. 1904.
51. Bongers: Ü. Synthesen im Organismus der Vögel. C. m. W. **1889.** 238.
52. Marriott and Wolf: The Metab. in Brombenzol Poisoning. Amer. Med. **9.** 1026. 1905.
53. Patten: Über Cystin. Z. p. C. **39.** 350. 1903.
54. Neuberg u. Manasse: Die Isolierung der Aminosäuren. B. C. G. **38.** 2359. 1905.

II.—THE EXCRETION OF DIAMINES.

1. Occurrence.

The occurrence of diamines in urine was discovered by Baumann and von Udránzki (1) in a case which was at the same time cystinuric; it has also been recorded by many other observers (2 to 6).[1]

These diamines are tetramethylene-diamine or putrescine—

$$\begin{array}{l} CH_2—CH_2 \cdot NH_2 \\ | \\ CH_2—CH_2 \cdot NH_2, \end{array}$$

and pentamethylene-diamine or cadaverine—

$$CH_2\begin{array}{l} \diagup CH_2—CH_2 \cdot NH_2 \\ \diagdown CH_2—CH_2 \cdot NH_2. \end{array}$$

[1] Cohn failed to find diamines in his case.

According to L. Brieger, there appears yet a third diamine,[1] saprine or neuridine, which is isomeric with cadaverine; but little is known about the excretion of this diamine. Cadaverine and putrescine may occur together or separately. L. von Udránzki and E. Baumann (1) were able to isolate about 0·2 to 0·4 gramme per day of diamine as dibenzoyl derivatives. At first both diamines were found—namely, about one-third tetramethylene-diamine and two-thirds pentamethylene-diamine; later, and in the same case, Garcia (7) was only able to prove the presence of putrescine. In Brieger and Stadthagen's case only cadaverine was found.

In the examples of simultaneous cystinuria and excretion of diamines, the latter are not only found in the urine, but they are likewise frequently present in the fæces; and Roos (8) has shown them to be present in the fæces only in cholera, severe gastro-enteritis, in malaria and dysentery (9).

It has never been found possible to obtain diamines either from the fæces, the urine,[2] or the blood of normal persons; but, according to Werigo (10), pentamethylene-diamine is to be found in pancreatic extracts, and Steyrer (11) isolated the same base from the mixture of substances which are formed during aseptic autolysis of the same organ. Moreover, the statement of Lawrow (12) that cadaverine and putrescine appear on very intense and long-continued pepsin digestion (gastric autodigestion), and probably arise from the diamino-acids, is of importance.[3]

Brieger (13) has identified the diamines as products of true protein putrefaction, and, in fact, determined that they are abundantly formed by definite micro-organisms, such as the comma bacillus or the Finckler-Prior bacillus.

2. Origin of Diaminuria.

In cases of acute intestinal disturbance the bacteria which are then active may be considered as the agents which produce the diamines, for these are products of the metabolism of the micro-organisms.

But in cystinuria accompanied by diaminuria the circumstances are different. Baumann and Udránzki (1) have assumed the intestinal origin of such diaminuria also. Cadaverine and putrescine were due to a chronic intestinal mycosis, and after resorption gave rise to cystinuria.

[1] Brieger obtained two ptomaines isomeric with cadaverine from human flesh which had been left to putrefy at the ordinary temperature for three to eleven days. These he named neuridine and saprine. Neuridine he also found in the fresh human brain and in considerable quantity in putrid horseflesh. L. von Udránzki and E. Baumann (*loc. cit.*) thought they had found one of these isomers of cadaverine in their case. They had hydrolyzed a large quantity of dibenzoylcadaverine without first obtaining it perfectly pure, and on preparing the platinum double salt, they found in the mother-liquor what appeared to be a more soluble isomer. By precipitating with alcohol and recrystallizing the precipitate, it was shown to be only the cadaverine double salt; and on benzoylating the last mother-liquor, they obtained only dibenzoylcadaverine.

[2] Dabrowski found traces of cadaverine in 100 litres of normal urine (*Maly's Jahresberichte*, 1903, vol. xxxiv., 468).

[3] It is not certain that the action of putrefactive bacteria was fully excluded in all these cases (*cf.* vol. i., p. 12).

Conversely, Garcia (7) considered in all seriousness that tetramethylene-diamine might be derived from cystin itself, but that the latter might also be formed by decomposition from pentamethylene-diamine (!).

Various objections may be raised against these views. There is more probability in the assumption that ultimately similar or even identical causes underlie both cystinuria and diaminuria—namely, disturbances of protein metabolism of varying degrees [Loewy and Neuberg (14)]. The anomaly results, if it is only slight in character, merely in an excretion of cystin, but if it has progressed further, in diaminuria as well; however, the observations of Werigo, Steyrer, and Lawrow (10, 11, 12) show that when the digestive processes are deranged diamines may occur. On this view it is intelligible that, in many cases, cystinuria occurs without excretion of cadaverine and putrescine, and that of these bases one or both may gradually vanish, while the cystinuria persists. The converse condition is never observed.

The suggestion of Brieger (13) that the diamines are products of protein decomposition has been verified by Ellinger (15), who succeeded in proving that lysin is the direct mother-substance of cadaverine and arginin, or diamino-valerianic acid of putrescine. The diamino-acids, when isolated, pass—chiefly by anaerobic putrefaction—into diamines by loss of carbon dioxide, and the same reaction has been effected in a purely chemical manner by Neuberg (16).

To all appearance diaminuria and cystinuria form an allied group of disturbances of the normal transformation of protein; they depend on an anomaly of amino-acid metabolism which involves the sulphur-containing complex with relative frequency, the basic fractions less often, and which may even, in some instances, implicate other protein fractions.

3. Experimental Diaminuria.

By the administration of diamines von Udránzki and Baumann (1) were able to bring about an excretion of diamines. While small quantities were completely oxidized, after feeding with 3 grammes putrescine hydrochloride, 0·056 gramme of dibenzoyl-putrescine, and after 10 grammes of cadaverine acetate, 0·722 gramme of dibenzoyl-cadaverine were obtained from the urine, and in the latter case 0·165 gramme from the fæces.

In a case of cystinuria unaccompanied by diaminuria, the latter could be artificially produced by feeding with diamino-acids, and, in fact, putrescine and cadaverine passed into the urine after feeding with arginin and lysin respectively; no diamines could be detected in the fæces [Loewy and Neuberg (14)]. As these experiments were made without evading the intestinal canal, they do not of themselves exclude a bacterial formation of diamines from diamino-acids in the digestive tract. Such a formation is, however, improbable when it is considered that the case of cystinuria in question has been long under observation, has been without chronic diaminuria, and that the normal food, which always contains diamino-acid complexes, has never occasioned the

formation of these bases. This artificial diaminuria probably appears, like the natural diaminuria in cystinuric cases, owing to definite disturbances of the normal protein transformation.

4. Significance of Diaminuria.

The chronic diaminuria accompanying cystinuria is, like cystinuria itself, of an entirely harmless nature ; it is, like alkaptonuria and certain of the rarer disturbances in carbohydrate metabolism, a constitutional anomaly which appears to be unimportant as regards the health of the person affected.

When the diamine formation is brought about by definite specific excitants, the circumstances may be different. Baumann and Udránzki have attached great importance to the form in which the diamines appear in the intestines, and have assumed a distinction according as the diamines are present as salts or free bases, because the latter especially are supposed to irritate the mucous membrane of the digestive tract and exert a toxic action. But, on the other hand, Roos (9) found that in his cases of grave intestinal disease accompanied by excretion of diamines there was persistent acid reaction of the stools. The share to be allotted to the diamines as such in the virulence of these diseases is uncertain.

Still, as Pohl (17) has shown, the diamines are never quite without poisonous action, and whether their prolonged appearance is quite unimportant for the organism must, in view of Pohl's experiments on the checking of important physiological syntheses—the formation of hippuric and conjugated glycuronic acids—by diamines, remain a subject for discussion.

It is, moreover, uncertain whether the diamines are related (physiologically ?) to the chemically allied Schreiner's base spermine and the Leyden-Charcot crystals, both of which are presumably cyclic diamines.

5. Recognition of Diaminuria.

The diagnosis of diaminuria depends on the isolation of the respective bases. This can be effected after the method of von Udránzki and Baumann by benzoyl chloride and caustic alkali (1), after that of Brieger by mercuric chloride or picric acid (13), or after that of Loewy and Neuberg (18) by phenyl isocyanate.

LITERATURE.

1. Udránzki u. E. Baumann : Ueber das Vorkom. von Diaminen bei Cystinurie, etc. Z. p. C. **13.** 562. 1889 ; and **15.** 81. 1891.
2. Brieger u. Stadthagen : Beirt. zur Kenntnis der Zusammensetz. des Mytilotoxins, etc. Ar. p. A. **115.** 490. 1889.
3. Cohn : Ueber familiäre Cystinurie. B. k. W. **1899.** 503.
4. Cammidge and Garrod : On the Excretion of Diamines in Cystinuria. Ma. **30.** 904. 1900.
5. Simon : Cystinuria. A. J. M. S. **119.** 39 ; **123.** 838. J. H. H. Bulletin. **15.** 365.

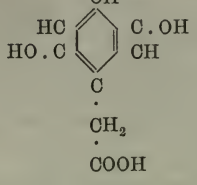
6. Marriott and Wolf: Cystinuria. A. J. M. S. **1906.** Feb.
7. Garcia: Ueber Ptomaïne. Z. p. C. **17.** 577. 1893.
8. Roos: Ueber das Vorkom. von Diaminen bei Cholera und Brechdurchfall. B. k. W. **1893.** Nr. 15. P. 354.
9. Roos: Ueber das Vorkom. von Diaminen bei Krankheiten. Z. p. C. **16.** 192. 1891.
10. Werigo: Ueber das Vorkom. des Pentamethylendiamins in Pankreasinfusen. Ar. P. M. **51.** 362. 1892.
11. Steyrer, see Emerson: Ueber das Auftreten von Oxyphenyläthylamin bei der Pankreasverd. und über ferment. CO_2-Abspaltung. Be. P. P. **1.** 506. 1902.
12. Lawrow: Zur Kenntnis des Chemismus der pept. und trypt. Verdauung der Eiweisskörper. Z. p. C. **33.** 312. 1901.
13. Brieger: Über Ptomaïne. 1885.
14. Loewy u. Neuberg: Ueber Cystinurie. Z. p. C. **43.** 338. 1904.
15. Ellinger: Die Konstitution des Ornithins und Lysins. See Beitr. zur Chem. der Eiweissfäulnis. Z. p. C. **29.** 334. 1900.
16. Neuberg: Eine neue Synthese der Diamine. Ibid. **45.** 110. 1905.
17. Pohl: Synthesenhemmung durch Diamine. Ar. P. P. **41.** 97. 1898.
18. Loewy u. Neuberg: Zur Kenntnis der Diamine. Z. p. C. **43.** 355. 1904.

III.—ALKAPTONURIA.

1. General.

Alkaptonuria was discovered in 1859 by Boedeker (1). It is characterized by the presence in the urine of aromatic substances of an acid nature, which combine with great avidity with alkalis, with simultaneous absorption of oxygen. The darkening which occurs when these substances are treated with an alkali has given to these bodies the name "alkapton acids," and to the anomaly the designation "alkaptonuria." The alkapton substances were examined subsequently by Ebstein and Müller (2), and regarded as pyrocatechin. After various failures by other workers, Wolkow and Baumann (3) succeeded in 1891 in isolating an alkapton body. It proved to be hydroquinone-acetic acid (I.), a derivative of an isomer of pyrocatechin called hydroquinone. Soon afterwards this compound was prepared synthetically[1] by Baumann and Fränkel (4), starting from gentisic aldehyde (II.). On account of the relationship to this substance, it has since borne the name "homogentisic acid."

I.



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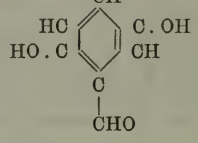
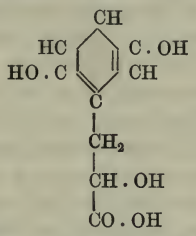


[1] Homogentisic acid has also been synthesized by W. A. Osborne (*J. P.*, 1903, vol. xxix., *Proc. Physiol. Soc.*, pp. xiii., xiv.) by condensing hydroquinone dimethyl ether with ethyl monochloracetate in carbon disulphide solution by means of aluminium chloride, and

Homogentisic acid has been found in all cases of alkaptonuria. In addition, a second aromatic dioxy-acid found by Kirk (5) is also occasionally present. The same substance was again observed at a later date by Huppert (6), and by Langstein and Meyer (7). They found it occasionally only, and in very small quantity, along with the homogentisic acid. It was named by its discoverer "uroleucic acid." Its composition corresponds to a dioxyphenyllactic acid, but its precise constitution is not known. Usually, the following formula (hydroquinone lactic acid) is assumed for it, chiefly on the grounds of analogy :[1]



It is uncertain whether uroleucic acid occurs only in exceptional cases, or whether it ordinarily accompanies homogentisic acid in such small amounts that in most cases it remains undetected.

The blackening or browning of alkapton urine which has been mentioned occurs slowly also in air, even without the addition of alkali—in fact, in consequence of change of reaction, or of formation of ammonia, cases are known in which the freshly passed urine was coloured brown, and left stains on linen which were difficult to remove, a behaviour which has led in several cases to the discovery of the anomaly.

The strong reducing power of alkapton urine for alkaline copper and ammoniacal silver solutions is, moreover, characteristic ; but in contrast with urine containing sugar, which also shows this behaviour, it neither ferments nor rotates. Since the alkapton acids are phenolic in character, they give with dilute ferric chloride a blue or green colour respectively. Millon's reagent is not typical, for there results an orange-yellow, and not a red, precipitate, which only reddens on boiling.

The alkapton bodies may be isolated by extracting the acidified solution with ether, and also by precipitation with subacetate of lead.[2]

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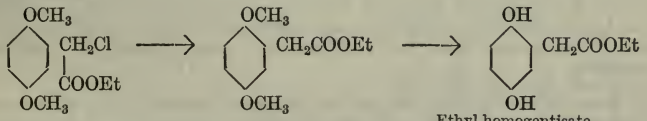
removing the methyl groups from the resulting ether by amorphous phosphorus and hydriodic acid:



Ethyl homogentisate.

[1] The lack of rotatory power in the compound is an argument against the formula assumed, as it contains an asymmetric carbon atom, and an optically active form of such a compound might be expected to occur in the organism.

[2] A. E. Garrod (*J. P.*, vol. xxiii., 512, 1899) has described a very simple method of isolating homogentisic acid from urine. A quantity of the urine, not less than 100 c.c., is heated nearly to boiling, and for every 100 c.c. from 5 to 6 grammes of solid neutral lead acetate are added. The precipitate thus formed must be filtered while the liquid is still hot. On standing in a cool place good crystals of the lead salt are obtained ; the crystallization is as complete as possible (by this method) in twenty-four hours.

The uroleucic acid is only precipitated in strong solution in this way.

In pure condition both the alkapton acids are colourless crystalline substances. Homogentisic acid melts at 146·5° to 147°, and uroleucic acid at 130·5°.

2. The Alkapton Excretion.

Alkaptonuria has been observed at different periods of life. In some cases it was certainly inborn, and, like pentosuria and cystinuria, has been observed in children of the same parents [Kirk (5), H. Embden (8), A. E. Garrod (9), and O. Schumm (11)], and in children of parents related by blood[1] [Garrod and Meyer (10)].

The quantity of alkapton acids excreted oscillates between 0·2 and 0·4 per cent., amounting, therefore, to about 3 to 6 grammes per day [Wolkow and Baumann (3)]. The determinations undertaken by Falta and Langstein (12), and those by Neubauer and Falta (13), vary within the same limits. Somewhat higher values—up to 7 grammes per day—were found occasionally by Langstein and Meyer (7), while the highest excretion[2] ever observed was 16·8 grammes by O. Schumm (11).

The anomaly is in most cases chronic, and persists throughout life, apparently without injury to the subject. But transitory symptomatic forms have been observed occasionally in diabetes [A. Geyger (14)], in cirrhosis of the liver, tuberculosis [von Moraczewski (15)], pyonephrosis [A. Slosse (16)], gastric catarrh,[3] etc. (*cf.* also 17). A causal connection of alkaptonuria with the other conditions has not been proved. Albrecht and Zdarek (18) conjecture that the peculiar browning of the cartilage in ochronosis may have some relation to alkaptonuria, but Langstein (19) could not ascertain the presence of alkapton acids in the urine of a person affected with ochronosis[4] [*cf.* L. Pick (20)].

Bandel (21) has recently published the observation that in a case of this anomaly the cerumen was of a deep brown colour.[5]

[1] A. E. Garrod (*Lancet*, 1902, vol. ii., 1616) was the first to observe that among alkaptonurics a relatively large proportion were children of first cousins. Meyer's case was one of these.

[2] The largest quantity of homogentisic acid excreted in one day is recorded by Zimper (*Inaug. Diss.*, Würzburg, 1903). The daily average excretion of this patient amounted to 16·56 grammes on his normal diet, but on giving him three tablespoonfuls of "tropon" he excreted 23·09 grammes. Schumm's patient excreted on an average 7·5 grammes on a mixed diet; on one day he excreted 16·8 grammes, but on the two preceding days he had been given a rich meat diet and 70 grammes of casein each day, while on the day in question the casein had been replaced by "nutrose." Falta estimates that the tyrosin and phenylalanine in 100 grammes of casein would, if completely converted into homogentisic acid, yield 7·23 grammes. It will be seen that Zimper's figures are surprising.

[3] C. Hirsch, *B. k. W.*, 1897, 866.

[4] E. Stier (*B. k. W.*, 1898, 185) noticed that the aural wax in his alkaptonuric had a deep brown colour, and he thought the coloration might be due to homogentisic acid. He washed out the ears of his patient weekly for a month, evaporated the washings with a little sulphuric acid, and extracted the residue with ether. On evaporation of the ether, the residue gave distinct darkening with caustic soda, but the reduction of ammoniacal silver solution could not be proved. Stier, by taking 6 grammes of homogentisic acid, confirmed Embden's account of the action of the acid on normal persons. While it is certain that not all cases of ochronosis are due to alkaptonuria, W. Osler (*Lancet*, January 2, 1904) has described pigmentation of the skin and of the aural cartilages in some elderly alkaptonurics.

[5] From the brief account available (five lines !) it is not clear how far the connection between the anomaly and the coloration of the cerumen is proved.

3. The Relationship of Alkaptonuria to Protein Metabolism—Theory of Alkaptonuria.

As with pentosuria, the interest of alkaptonuria is more theoretical than practical, because this anomaly has enabled us to obtain important glimpses at a particular chapter of protein transformation.

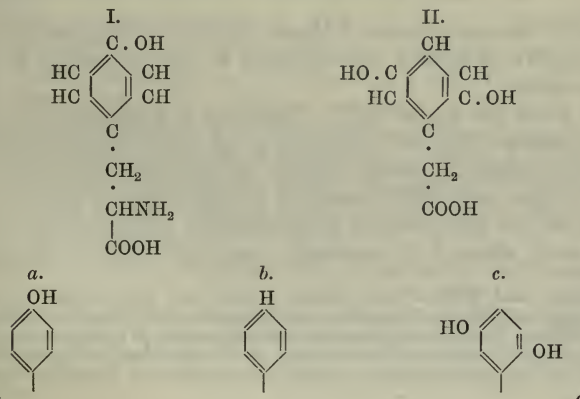
The chemical nature of the alkapton bodies—in particular, the fact that they belong to the aromatic series—soon prompted the thought that they were related to the cyclic members of the protein molecule. The first experimental test of this conjecture immediately confirmed its accuracy.

Baumann and Wolkow (3) found, in fact, that pure tyrosin is transformed in the organism of an alkaptonuric almost quantitatively into homogentisic acid. After administration of 10 grammes of oxyphenylaminopropionic acid (tyrosin) by the mouth, they obtained 7·5 grammes of homogentisic acid in the urine—that is, more than 80 per cent. of the theoretically possible quantity. Mittelbach (17) found that 93·5 per cent. of administered tyrosin appeared as homogentisic acid in the urine.

Other experiments made about the same time point to a connection between the alkapton acids and the aromatic group of the proteins. Ogden (22) and also P. Stange (23) showed that with an exclusively protein diet the quantity of alkapton bodies is from about one-quarter to about one-half greater than it is with a mixed diet.

On the ground of this discovery, Baumann and Wolkow did not hesitate to consider alkaptonuria as an anomaly in the metabolism of the aromatic group in protein, and particularly of the tyrosin, and they developed from this circumstance the following conception.

The constitution of tyrosin (I.) on the one hand, and of homogentisic acid (II.) on the other hand, is such that a direct formation of the alkapton substance from the protein-splitting product is impossible. The transformation is, however, effected by specific bacteria in the intestinal canal of the alkaptonuric individual. In this way the phenolhydroxyl group (*a*) first experiences a reduction (*b*), and the introduction of two hydroxyl groups which then follows is quite analogous to the well-known transformation of benzene itself into hydroquinone (*c*).



It is seen that this suggested explanation of alkaptonuria seizes on a similar auxiliary hypothesis to that which was developed in his time by Baumann for cystinuria, and just as little has it withstood a severe criticism. The results of experiments made shortly afterwards by Baumann's pupil, Embden (8), were opposed to the formation of homogentisic acid by abnormal and specific bacteria ; for he failed to influence the supposed bacterial activity and the alkaptonuria by means of various disinfectants introduced into the digestive tract.

Real progress in the knowledge of the nature of alkaptonuria has, however, only been made by making exact experiments on the metabolism in this anomaly. By means of such experiments Mittelbach (17) first struck a decisive blow at the theory of the intestinal origin of homogentisic acid. It clearly follows from his fasting experiments that the excreted alkapton acids were not derived from the protein of the food alone, but from the protein of the organs as well. Mittelbach found for the day's amount of alkapton acids 4·66 grammes on a full diet ; on abstracting the protein it still amounted to 2·97 grammes, and even during fasting it remained at almost half of the original value—namely, at 2·57 grammes. Langstein and Meyer (7) then showed that on an exclusively fat carbohydrate diet the alkapton acids in the urine did, in fact, diminish, but never vanished. Thus it follows, just as from Mittelbach's fasting experiments, that the alkapton acids can be formed from the protein of the organism.

Thus alkaptonuria is shown to be a metabolic anomaly brought about by unusual changes in the tissues, and of quite a different significance from a phenomenon due to foreign organisms in the intestinal canal, and not in a strict sense within the organism.

Now, a simple calculation shows that the transformed tyrosin complex of the body protein could not possibly account for the whole amount of the homogentisic acid excreted, for the tyrosin content of the ordinary proteins is much too small, and leads to the necessity of taking another aromatic radical into consideration.

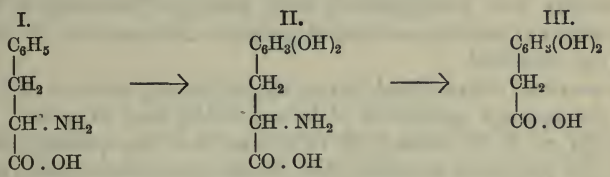
To a similar result led an experiment with a casein diet in which the preformed tyrosin could only just yield the amount of homogentisic acid formed.

Further, the experiments of Meyer, Falta, and Langstein have yielded extraordinarily important contributions to the knowledge of the origin of alkaptonuria.

First, there was found[1] by W. Falta and L. Langstein (12) the second aromatic residue that was required in phenylalanine (phenylaminopropionic acid), which is closely related to oxyphenylaminopropionic acid (tyrosin). The naturally occurring *l* form was transformed in the organism of the alkaptonuric approximately quantitatively into homogentisic acid, whereas the optically inactive racemic form appeared to

[1] Baumann and Wolkow had already pointed out that, besides tyrosin, phenylalanine might possibly be taken into consideration as the mother-substance of the alkapton bodies. Embden (8), however, on the ground of experiments with phenylglycocoll and phenylacetic acid, had arrived at the view that no hydroxyl-free benzene derivative, not even phenylalanine, could take part in the formation of homogentisic acid.

be able to yield about 50 per cent. of homogentisic acid, corresponding to its content of 50 per cent. of *d*-phenylalanine, which is foreign to the body. But Falta (24) found later that racemic phenylalanine was transformed up to 86·5 per cent. into homogentisic acid, so that the special configuration could have no influence on the alkapton formation. This behaviour is surprising, inasmuch as Wohlgemuth (25) has established for a series of other amino-acids that the antipode of the naturally occurring form passed the organism, and appeared in the urine. Evidently the circumstance of the absolute quantity plays a decisive part here, for Wohlgemuth found indeed that small quantities of amino-acids which are foreign to the body were destroyed in the organism, and only large quantities were excreted undecomposed. If, however, the transformation of the side-chain of phenylalanine (I.) by removal of the amino-group and oxidation occurs, as in the case of tyrosin, after preceding introduction of hydroxyl groups into the nucleus, then the asymmetry is lost, and there arises from the *d* and *l* form the same hydroquinone acetic acid—homogentisic acid (III.):



From researches on the fate of a large series of aromatic acids—some of them had already been found as transformation products of the aromatic groups by E. and H. Salkowski, and by M. Nencki and E. Baumann in the decomposition of proteins by bacteria—in the normal and alkaptonuric organisms Neubauer and Falta (13) arrived at the conclusion that the normal breaking down of the aromatic complex begins with the introduction of hydroxyl groups into the benzene nucleus at the 2 : 5 position, then proceeds to splitting of the benzene ring, and finally proceeds to total oxidation. Therefore the metabolic disturbance in alkaptonuria consists, according to Falta (24), in a complete incompetency to split up the hydroxyl-containing benzene ring any further. Supported by the statements[1] of M. Gonnermann (26), Czapek (27), and Bertel (28) that homogentisic acid is a normal breaking-down product of tyrosin and phenylalanine in plants, Falta assumes the occurrence of an analogous process in the animal organism, especially as Embden (8) had early established the almost complete combustibility of homogentisic acid in the normal human organism, and its resistance to combustion in the alkaptonuric individual.

Alkaptonuria depends, therefore, not on an abnormal formation of

[1] In a recently completed research, Schulze and Castoro (29) found themselves unable to confirm these statements as to the appearance of homogentisic acid in the metabolism of plants. Knoop (35) has thrown doubt upon the view that the breaking down of tyrosin and phenylalanine normally proceeds through the alkapton substances in the animal organism.

homogentisic acid, but on an incapacity for further dealing with it[1]—a condition which may be well compared with cystinuria.

The results of metabolic experiments in alkaptonuria harmonize with this view. The transformation of protein pursues exactly the same course as in a normal person; the nitrogen output is not disturbed. It is remarkable that the excretion of the alkapton bodies, which corresponds to a definite quantity of tyrosin and phenylalanin, takes place very much more quickly than the elimination of the nitrogen. This behaviour, which was established both by Falta by superposing pure protein substances on a standard diet, and by Langstein and Meyer (7) by following a diet poor in protein by one rich in protein, shows that the aromatic groups of protein substances are split off early, and after losing their amino-groups quickly pass into the urine of the alkaptonuric as homogentisic acid, while the excretion of nitrogen pursues a different and a slower course.

Alkaptonuria is so emphatically characterized as a disturbance of the metabolism of the aromatic group in protein that, under proper conditions of feeding, phenylalanin and tyrosin are transformed approximately quantitatively into homogentisic acid, although naturally a bacterial decomposition of small quantities of aromatic substances in the intestinal canal is not excluded.

This maximal character of the metabolic derangement is also brought out by the average quantities of homogentisic acid excreted. From a compilation of A. E. Garrod (9) it is seen that the quantity of homogentisic acid produced in twenty-four hours by adults is pretty constant, while that produced by children is correspondingly lower—that is to say, is always about as high as it can be with their respective mixed diets. The more recently observed cases[2] also dispose themselves in complete accordance with Garrod's scheme.

With the sharply marked dependence of the excretion of the alkapton bodies on the content of protein substances in the aromatic complexes, it is not to be wondered at that arbitrarily undertaken changes in these groups find their expression in terms of the output of homogentisic acid. In fact, W. Falta (24) was able to prove that neither dibromotyrosin,

[1] Garnier and Voirin (34) had already framed the hypothesis that the intermediate formation of homogentisic acid from tyrosin was a normal metabolic occurrence, but they did not furnish any experimental proof.

[2] Langstein and Meyer (*loc. cit.*) first determined the quotient, $\frac{\text{Homogentisic acid}}{\text{Nitrogen}}$. To avoid decimals the value of the quotient is usually multiplied by 100; it then means the number of grammes of homogentisic acid excreted per 100 grammes of nitrogen excreted. This H : N quotient is constant for a constant diet, but varies with the diet. On an ordinary mixed diet the quotient is 44. Falta (*loc. cit.*) found quotients of 54·6 and 21 for casein and egg-albumin respectively. These quotients correspond very well indeed with what they should be if the tyrosin and phenylalanin of the food are quantitatively converted into homogentisic acid. Now, if Garrod's theory of maximal alkaptonuria is correct, all alkaptonurics should yield the same quotient on "a standard diet of the simplest kind." All the cases available for testing this theory have been collected in a paper by A. E. Garrod and T. S. Hele (*J. P.*, 33, 198, 1905). The average values for four different cases were: (1) 44, (2) 44, (3) 40, (4) 49·6. The cases were (1) man, aged fifty years; (2) man, aged twenty years; (3) child, aged eight years; (4) child, aged four years. In the last case the diet was rather rich in nitrogen. Allowing for the circumstance that in no case was the diet the same, the quotients are remarkably similar.

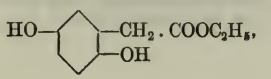
bromocasein, nor iodocasein, in all of which the halogen appears in the aromatic complex, form the alkapton bodies. This is, in fact, not surprising, for, from experiments by Mosse and Neuberg (30) with iodoalbumin, the aromatic complex is so changed by the entrance of iodine even for the normal organism that, instead of the ordinary oxidation products, *o*-iodobenzoic acid appears in the blood, and *o*-iodohippuric acid in the urine—at least, in the dog and rabbit.

As homogentisic acid is nothing but a metabolic product arrested at a stage short of complete decomposition, and one which is normally completely oxidized, the assumption that in alkaptonuria there is an impoverishment of the circulating protein in aromatic groups is improbable. Now, Falta and Abderhalden (31) have actually found that the blood proteins in alkaptonuria are normally constituted in respect of their content in tyrosin and phenylalanin ; only it must be said that the present methods are not equal to the recognition of those very nice distinctions which can alone be expected here. The authors mentioned proved the presence of homogentisic acid in the serum, so that by these results also alkaptonuria is shown to be independent of changes occurring in the intestine, in resorption, and in the kidneys.

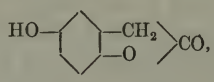
4. Diagnosis of Alkaptonuria.

In the general part the characteristic properties of the strongly reducing alkapton urine which led to the discovery of the anomaly have already been mentioned. It may be added that the urine in alkaptonuria possesses in most cases a considerable acidity. In spite of the relatively large quantity of homogentisic acid excreted, the ammonia content of the urine, as Meyer (10) has proved, is not increased, so that the alkaptonuria does not cause the phenomenon of acid-poisoning. Notwithstanding its close chemical relationship to the phenols, homogentisic acid neither forms an ethereal sulphate nor conjugates with glycuronic acid—a behaviour which harmonizes with its practical harmlessness.

In practice, the characteristic behaviour of the alkalized urine almost always suffices for the recognition of the alkapton acids. Homogentisic acid also gives a reaction with $FeCl_3$ which still produces a transitory blue coloration at a dilution of 1 : 4,000. With Millon's reagent there appears an orange coloration, but no reddening ; only on boiling does the yellow precipitate first formed take on a brick-red colour. For a more certain identification the lead salt $[(C_8H_7O_4)_2Pb + 3H_2O)]$, which melts at 214° to 215°, may serve ; but on account of the ease with which the lead salt decomposes, the determination of the characteristic melting-point, as well as of the water of crystallization, presents difficulties. Erich Meyer recommends the preparation of the ethyl ester of homogentisic acid—



which is difficultly soluble, and melts at 119°. On incomplete esterification, there may be formed as an intermediate product the lactone of homogentisic acid, the anhydride of the formula



which melts at 191°, and, in opposition to free homogentisic acid, gives a red colour with Millon's reagent, and in a solution made feebly alkaline by ammonia or soda an intense pale blue colour passing through dark violet to the characteristic alkapton shade.

Uroleucic acid, which is rarely present, may be extracted from the mother-liquor of the homogentisic acid. It exhibits similar reactions, and melts at 130·5°.

The quantitative determination of the alkapton acids in urine is carried out, according to E. Baumann (32), by titration with ammoniacal $\frac{N}{10}$ silver solution, of which 1 c.c. corresponds to 0·004124 gramme homogentisic acid (No separate method is known for the determination of uroleucic acid.)[1] A slightly modified procedure, but one resting on the same principle, has been described by G. Denigès (33).

The reducing power of alkapton urine may be considerable. It is, according to Denigès, about nine to ten times as strong as that of a diabetic urine of the same percentage strength for Fehling's solution and for silver solution.

There is an important practical point about this strong reducing power of homogentisic acid, inasmuch as this behaviour may lead to its being mistaken for sugar, and it has been so mistaken before now [Garnier and Voirin (34)]. Nevertheless, the inability to undergo fermentation, and the lack of optical activity, easily permit of a distinction between the alkapton bodies and glucose.

Treatment.

No treatment for alkaptonuria is known, and, indeed, considering that the metabolic disturbance is harmless, and involves no danger to the patient, treatment is hardly necessary. Of course, the dark stains sometimes caused in the linen by alkapton urine are somewhat troublesome.

[1] In his method of estimating homogentisic acid Baumann recommends the addition of 3 per cent. ammonia to the urine before adding the $\frac{N}{10}$ silver nitrate. But he states in a later paper that his number 1 c.c. = 0·004124 gramme homogentisic acid was obtained by using ammonia of from 8 to 10 per cent. strength. A. E. Garrod and W. H. Hurtley (*J. P.*, 33, 206, 1905) showed that the reduction of silver is not complete when 3 per cent. ammonia is used. It follows that all estimations carried out by Baumann's method will give low results for the homogentisic acid. While such results can be compared with one another with safety, they give values for the absolute amount of the acid which are from 11 to 12 per cent. too low.

LITERATURE.

1. Boedeker: Z. r. M. [3]. **7.** 138. 1859.
2. W. Ebstein u. J. Müller: Brenzkatechin im Urin eines Kindes. Ar. p. A. **62.** 554. 1875.
3. M. Wolkow u. E. Baumann: Ueber das Wesen der Alkaptonurie. Z. p. C. **15.** 228. 1891.
4. Baumann u. Fränkel: Ueber die Synthese die Homogentisinsäure. Z. p. C. **20.** 219. 1894.
5. Kirk: B. M. J. **1886.** II. 1017; **1888.** II. 232; **1889.** II. 1149.
6. Huppert: Ueber die Alkaptonsäuren. Z. p. C. **23.** 412. 1897.
7. Langstein u. Meyer: Beitr. zur Kenntnis der Alkaptonurie. D. Ar. M. **78.** 161. 1903.
8. Embden: Beitr. zur Kenntnis der Alkaptonurie. Z. p. C. **17.** 182. 1892; **18.** 304. 1893.
9. Garrod: L. **1902.** Dec. 13.
10. Meyer: Ueber Alkaptonurie. D. Ar. M. **70.** 443. 1901.
11. Schumm: Beitr. zur Kenntnis der Alkaptonurie. Mü. m. W. **1904.** Nr. 36.
12. Falta u. Langstein: Die Entsteh. der Homogentisinsäure aus Phenylalanin. Z. p. C. **37.** 513. 1903.
13. Neubauer u. Falta: Ueber das Schicksal einiger aromat. Säuren bei der Alkaptonurie. Z. p. C. **42.** 81. 1904.
14. Geyger: Pharm. Ztg. **37.** 488. 1892.
15. Moraczewski: C. i. M. **1896.** Nr. 7.
16. Slosse: Un nouveau cas d'alcaptonurie. C. m. W. **1895.** 684.
17. Mittelbach: Ein Beitr. zur Kenntnis der Alkaptonurie. D. Ar. M. **71.** 50. 1901.
18. Albrecht u. Zdarek: Ueber Ochronose. Z. H. **23** [3]. 366, 379. 1902.
19. Langstein: Zur Kenntnis der Ochronose. Be. P. P. **4.** 145. 1904.
20. L. Pick: Ueber die Ochronose. B. k. W. **1906.** Nr. 16 *et seq.*
21. Bandel: Ueber Alkaptonurie. D. m. W. **1906.** Nr. 12. P. 487.
22. Ogden: Ein Fall von Alkaptonurie. Z. p. C. **20.** 280. 1894.
23. Stange: Ueber einen Fall von Alkaptonurie. Ar. p. A. **146.** 86. 1896.
24. Falta: Der Eiweiss-stoffw. bei Alkaptonurie. Habilitationsschr. 1904.
25. Wohlgemuth: Ueber das Verhalten stereoisomer Substanzen im Tierkörper. B. C. G. **38.** 2064. 1905.
26. Gonnermann: Homogentisinsäure. Ar. P. M. **82.** 289. 1900.
27. Czapek: Ber. d. D. botan. Ges. **20.** 1902; **21.** 1903.
28. Bertel: Ibid. **20.** 454. 1902.
29. Schulze u. Castoro: Bildet sich Homogentisinsäure beim Abbau des Tyrosins in den Keimpflanzen? Z. p. C. **48.** 396. 1906.
30. Mosse u. Neuberg: Ueber den phys. Abbau von Jodalbumin. Z. p. C. **37.** 427. 1903.
31. Abderhalden u. Falta: Die Zusammensetz. der Bluteiweiss-st. in einem Falle von Alkaptonurie. Z. p. C. **39.** 143. 1903.
32. Baumann: Ueber die Bestim. der Homogentisinsäure im Alkaptonharn. Z. p. C. **16.** 268. 1891.
33. Denigès: Ueber einen bemerkenswerten Fall von Alkaptonurie. Jo. P. [6]. **5.** 50. 1897.
34. Garnier u. Voirin: Ar. P. [5]. **4.** 225. 1892.
35. Knoop: Der Abbau aromat. Fettsäuren im Tierkörper. Be. P. P. **6.** 150. 1905.
36. Minkowski: Über Alkaptonurie. M. K. **1907.** S. 4.

CHAPTER XII

OXALURIA

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Translated by W. H. Hurtley, D.Sc. (Lond.).

1. General.

Oxalates always constitute a part of the organic substances which are excreted in the urine. Under the name " oxaluria " are comprised certain irregularities in the excretion of oxalates. These irregularities are not of a uniform character, nor are they always obviously due to nutritional disturbances. The designation of the conditions referred to—at the present time it is, perhaps, no longer quite appropriate to conceive of them as a separate metabolic anomaly in the strict sense of the word—has descended from a time when Prout (1) referred such clinical symptoms as those of neurasthenia and derangements of digestion to the existence of oxaluria.

This idea has not held its own in the light of recent more precise investigations.

2. The Occurrence of Oxalic Acid.

Oxalic acid $\begin{pmatrix} COOH \\ | \\ COOH \end{pmatrix}$ is widely disseminated in vegetables, especially as calcium oxalate, $\begin{matrix} COO \\ | \\ COO \end{matrix}\!\!>\!Ca$, and acid potassium oxalate, $\begin{matrix} COOH \\ | \\ COOK \end{matrix}$ (salts of sorrel). In the urine it occurs, too, as salts, principally as calcium and magnesium salts. Of these, when pure, the first is insoluble, and the second soluble with difficulty in water. According to Buchheim and Piorkowski (2), soluble alkaline oxalates also occur in urine. The oxalate sediment principally consists of calcium oxalate, which is dimorphous and crystallizes in plates belonging to the monoclinic system, and in octahedra belonging to the tetragonal system. The first of these two crystalline forms is the monohydrated salt $CaC_2O_4 . H_2O$; the second is the trihydrated salt $CaC_2O_4 3H_2O$.

The quantity of oxalic acid present as sediment is far from being a measure of the actual amount of the acid in urine. Lately Klemperer and Tritschler (3) have been able to prove conclusively in numerous cases a fact which had already been emphasized by Fürbringer (4)—that a

urine may fail to yield a sediment, and yet be relatively rich in oxalic acid, and, conversely, a urine may yield an abundant sediment, and yet be relatively poor in the acid. For the separation of crystals, among which may be crystals of calcium carbonate as well as of oxalate [Dunlop (5)], depends less on the absolute amount of the acid than on certain physical and chemical factors—the acidity of the urine, the ratio of the bases calcium and magnesium with which the oxalic acid is combined to each other, and on the presence of alkalis.

That calcium oxalate, itself insoluble, might remain dissolved in urine was formerly referred to the acidity caused by acid sodium phosphate (6, 7). In reality, according to Klemperer and Tritschler (3), yet another factor[1] has to be considered—namely, the ratio of the lime to the magnesia. These authors showed that for the ratio CaO : MgO = 1 : 0·8 to 1 : 1·2, and with an absolute content of the urine in magnesia of about 0·02 per cent., the calcium oxalate remains entirely in solution. This was confirmed by Rosin (8).

These circumstances are of decisive importance for the question of the excretion of oxalic acid, and no value can be ascribed to the older estimates based entirely on the quantity of the sediment.

Besides its occurrence as salts, oxalic acid may also be present in urine in combination, conjugated with urea as oxaluric acid (H_2N . CO . NH . CO . COOH). Schunck (9) first observed preformed ammonium oxalurate in human urine in 1867, and Neubauer (10) confirmed his statement. Like the conjugated sulphates, oxaluric acid is hydrolyzed by hot dilute mineral acids, but, unlike them, its synthesis from its components is much more easily effected *in vitro*. Accordingly, the possibility that the urinary oxaluric acid was merely formed in the course of the operations necessary for its isolation was not excluded; the question was only decided in favour of its preformed occurrence by the researches of Salkowski (11) and Luzzatto (12).

The quantity of oxalic acid normally present in urine is only small. With ordinary diet the mean daily quantity amounts to 0·017 gramme according to Dunlop (5); Fürbringer (4) found 0·02 gramme per day; Autenrieth and Barth (13) give 0·015 gramme.

Small and variable quantities of oxalic acid are met with in the organs of men and animals. As already mentioned, the amount in many vegetables is by no means inconsiderable—a fact which has an important bearing on the question whether oxaluria occurs as a metabolic anomaly.

The content in oxalic acid of our commonest foods and beverages, etc., is approximately as follows: Cocoa, 4·5; tea, 3·7; sorrel, 3·6; spinach, 3·2; pepper, 3·2; rhubarb, 2·4; figs, 1·0; chocolate, 0·9; potatoes, 0·4; beetroot, 0·4; French beans, 0·2; coffee, 0·1; tomatoes, 0·05; cabbage, 0·2 [2]—all expressed in grammes per kilogramme. Cipollina (14) found in the organs of animals: Thymus, 0·025 to 0·012; spleen,

[1] The solubility of calcium oxalate in urine must be influenced by the amount of chlorine in the urine, and also by the amount of ammonia and of the alkali metals. Calcium oxalate is more soluble in water containing magnesium chloride and calcium chloride than it is in water alone; also a number of soluble double oxalates, such as $K_2Mg(C_2O_4)_2$, $(NH_4)_2Mg_3(C_2O_4)_4$, are known.

[2] These numbers are Esbach's (compare footnote next page).

0·018 ; lungs, 0·012 ; liver, 0·006 to 0·011—all in grammes per kilogramme, and only traces in muscle.

For further estimates see Esbach[1] (15), E. Salkowski (39), N. Stradomsky (16), G. Pierallini (17), and A. M. Luzzatto (12).

3. Origin of Oxalic Acid.

Oxalic acid is quite commonly met with as the final product of oxidation in chemical processes of the most varied kind. Oxalic acid may also appear in the organism as a final product of oxidation, but, as the researches of the last few years have shown, besides the formation of the acid by oxidation, we must also admit its origin from that already present in the food. Thus two sources of oxaluria must be considered.

(*a*) *Alimentary Oxaluria.*

Even to-day, in spite of many researches directed expressly to this subject, it is undecided whether oxalic acid is at all susceptible of a real combustion in the tissues of the organism ; but that at least a part is excreted unchanged is proven.

It is certain that the output and intake of oxalic acid do not run parallel, but the reasons for this are very evident ; for the excretion depends upon that part of the quantity taken which is absorbed [G. Pierallini (17), Leignes Bakhoven (52)].

Of the oxalic acid which is present in the food in an insoluble form as calcium salt—and the greater part of it is in this form—that portion, at most, can be absorbed which is transformed into the soluble condition in the digestive tract. This transformation is effected in part by the gastric juice ; but the part not absorbed in the stomach and in those sections of the intestines having an acid reaction will be retransformed into unabsorbable, insoluble calcium oxalate by the alkalis and never-failing calcium salts of the intestines. This calcium oxalate, along with soluble, but also unabsorbed, quantities of oxalates will then, according to Stradomsky (16) and to Klemperer and Tritschler (3), be in part destroyed by intestinal putrefaction. This harmonizes with what has been found by Dunlop (5), Mohr and Salomon (18), and Rosenqvist (19)—namely, that oxaluria can be increased or diminished by the administration of acids or alkalis respectively ; it harmonizes, too, with Gaglio's (20) observation that soluble oxalates, when subcutaneously injected, pass almost quantitatively into the urine.

Rabbits are able to completely absorb and destroy doses of 1 gramme of oxalic acid given as sodium salt per day [Autenrieth and Barth (13)].

O. Minkowski (21), accurately apprising these circumstances, has given expression to the view that oxalic acid $\begin{pmatrix} O=C-OH \\ | \\ O=C-OH \end{pmatrix}$, like phosphorus (P) and carbon monoxide (CO), when once absorbed, undergoes

[1] Esbach's data were obtained by the older and less trustworthy methods of determining oxalic acid, and are, therefore, not exact.

no further change by the oxidative processes of the human organs. All these substances have one point in common—namely, an absence of hydrogen atoms directly united to the oxidizable element (P or C), such atoms being, according to Schmiedeberg, indispensable for the occurrence of oxidation.

The quantities of exogenous oxalic acid which appear in human urine are naturally variable, corresponding to the unequal amounts of the acid in the vegetable food, and to the transitory physiological conditions.

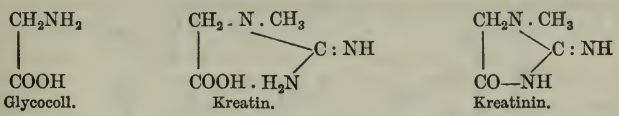
Obviously the excretion of oxalic acid in the urine is necessarily dependent on what occurs in the digestive tract. If earlier authors regarded functional and nervous disturbances of the digestive apparatus as a consequence of oxaluria, then they did for the most part but confuse cause and effect.

(*b*) *The Excretion of Oxalates of Endogenous Origin.*

Twenty-one years ago Wesley Mills (22), in a research carried out under Salkowski's guidance, showed that even on a vegetable-free diet with exclusively flesh food oxalic acid occurs in the urine, a result also arrived at by Auerbach (23), working under somewhat different experimental conditions. On a pure milk and sugar diet, H. Lüthje (24) also observed the excretion of oxalic acid, and he found that even during fasting oxalic acid had not disappeared from the urine on the twelfth day.

The observation that a diet rich in protein brings about a relatively high excretion of oxalic acid suggested the idea that the true antecedents of oxalic acid must be sought among the proteins and the products of their hydrolysis. In fact, Lommel (25) found an increase of oxaluria after administration of gelatin; he considered gelatin, or the connective tissue which yields it, as the chief source of oxalic acid.

Whilst Rosenqvist (19) was unable to confirm Lommel's results, Stradomski (16), and also Mohr and Salomon (18), arrived at the same view as Lommel with respect to the oxalic acid forming power of gelatin. Klemperer and Tritschler (3) showed that amino-acetic acid (glycocoll), the most characteristic and most abundant product of the hydrolysis of gelatin, and also creatin (methylguanidin-acetic acid), which is allied to glycocoll, or creatinin, which is the anhydride of creatin, all bring about an increased excretion of oxalic acid:



Kühne, forty years ago, had conjectured that the two last-mentioned bases from flesh were antecedents of oxalic acid.

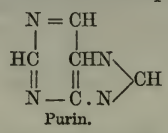
The results of purely chemical experiments might be drawn upon in

support of the gelatin theory, such as those of Kutscher and Schenck (26), in which abundance of oxalic acid and oxamic acid, $\begin{matrix}CONH_2\\|\\COOH\end{matrix}$, respectively were obtained by the oxidation of gelatin with permanganate; but as the experiments of Zickgraf (49), Otori (50), v. Fürth (27), and Seemann (28), have shown, oxalic acid and oxalic acid yielding complexes are quite commonly formed in the oxidation of protein substances *in vitro* —much more abundantly, indeed, than corresponds to the quantity of preformed glycocoll. Here oxalic acid is merely a final product of oxidation, just as it is in the case of carbohydrates and fats.

It was also due to considerations of a chemical nature that attention was early directed to another group of protein substances as the source of oxalic acid—namely, the nucleins, or, rather, the purins[1] contained in them. To the purins must now be added the pyrimidins[1] discovered by Kossel. These substances, of which the best-known representative is uric acid, easily yield, on chemical treatment outside the organism, oxalic acid[2] and its derivatives; also lower organisms, especially a fungus which often accompanies yeast, are said by Ranke (29) to decompose uric acid with formation of oxalic acid. As J. Pohl (30) has shown, in the case of ethylene glycol, $\begin{matrix}CH_2OH\\|\\CH_2OH\end{matrix}$, that suitably chosen substances of the two carbon atom series can be oxidized to oxalic acid, and as Wiener (31), in the case of alloxan (mesoxalylurea), $OC\begin{matrix}CO-NH\\\\CO-NH\end{matrix}>CO$, has done the same for definite compounds of the three carbon atom series allied to the pyrimidins,[3] the formation of oxalic acid by a process of oxidation is quite conceivable.

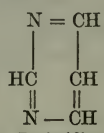
In fact, Wöhler and Frerichs (32) proved long ago that a copious oxalate sediment was caused in the urine of men and dogs on administration of purin bases, particularly urates, both by the mouth and subcutaneously. Gallois (33), Fürbringer (4), Lüthje (24), Salkowski (34), Stradomsky (16), Neubauer (6), either could not confirm these statements at all, or only in part. Luzzatto (12) suggests as an explanation that whilst it is certainly true that there are variations due to the individual, the contradictory results of earlier authors are to be referred partly to the lack of accurate methods of determination, and partly to the neglect of the oxalic acid present in the food. Luzzatto himself

[1] The parent substances of the purins and pyrimidins are:



Purin.

and



Pyrimidin.

[2] According to E. Salkowski (25), uric acid is oxidized even by ferric chloride, and thereby resolved into urea and oxalic acid.

[3] Alloxan may be regarded as an oxidized pyrimidin-tetraketo-dihydropyrimidin.

was unable to prove a true formation of oxalic acid from uric acid in the organism, but he regarded it as possible that oxalic acid might be formed as an intermediate product and then undergo further oxidation.

While Lommel (25), Lüthje (24), and Mohr and Salomon (18) arrived at no concordant results by experiments with combined purins, such as nucleins and nuclein-containing organs, Rosenqvist (19) showed that an increased excretion of oxalic acid hardly ever fails if the substances mentioned have really been resorbed. Rosenqvist, having found that pure gluton has no oxalic acid forming power at all, conceives that the positive results of other authors are due to the gelatin they employed containing nuclein.

But it is by no means certain that the normal oxidation of uric acid in the organism occurs by way of oxalic acid; quite other intermediate steps are conceivable. Glyoxylic acid, $\begin{vmatrix} CHO \\ COOH \end{vmatrix}$, the half aldehyde of oxalic acid, upon the physiological rôle of which attention has recently been directed by Eppinger (36), is perhaps one of these.

Glyoxylic acid, like oxalic acid, seems to occur in minimal quantities in urine. M. Almagia (37) showed that the excretion of glyoxylic acid is related to the metabolism of purins, and, according to Schloss (38), it is not impossible that glyoxylic acid passes into oxalic acid in the organism, and this, too, by its transformation in isolated organs (liver, brain).

That oxalic acid can actually be formed in the organs is shown by the digestion experiments of Salkowski (39), and of Klemperer and Tritschler (3). The former found that on adding uric acid to surviving liver oxalic acid is produced, while the latter obtained it on digesting uric acid with blood.

The carbohydrates, also, may be considered as precursors of oxalic acid. Zopf (40) has shown that definite saccharomyces set up a kind of fermentation in the ordinary mono- and disaccharides, and even in the alcohols, glycerin, mannite, and dulcite, in which oxalic acid appears in place of alcohol. The same power is possessed, according to Emmerling (41), by numerous ubiquitous bacteria—*e.g.*, staphylococci.

According to Paul Mayer (42) and H. Hildebrandt (43), more highly developed organisms are able to produce oxalic acid from glucose and from the closely allied compound glycuronic acid. On excessive administration of these substances by the mouth the amount of oxalic acid in the urine is increased, and likewise that in the organs—*e.g.*, in the liver, where Mayer (44) found extraordinary amounts of oxalic acid. The observation made by Mayer (*loc. cit.*) that the isolated liver, on digestion with glycuronic acid, forms oxalic acid is of special interest.

Baldwin (45) has not hesitated to make the carbohydrates jointly responsible for the formation of oxalic acid in the organism.[1] But Minkowski (21) rightly emphasizes the fact that it is doubtful how much of this oxalic acid formation is to be referred to simple fermentative changes in the digestive tract—that is, in a sense, outside the body—and

[1] Consult also Vol. I., p. 149.

how much to true tissue metabolism, and it cannot as yet be safely affirmed that oxaluria is actually an expression of a disturbance in the processes of oxidation [Reale and Boeri (46), Terray (47), Mayer, Hildebrandt].

Still, an endogenous origin of oxalic acid is certain, and, on the basis of the researches bearing upon it, *pathological significance* has been claimed for it in a large number of cases. Its literature[1] is wellnigh boundless, and there is scarcely a morbid condition in which an increased excretion of oxalic acid or formation of sediment has not been observed and commented on. But, apart from some more recent work (Salkowski, Mohr and Salomon, Lüthje, Cipollina, Stradomsky, Autenrieth and Barth, Luzzatto, P. Mayer, Minkowski and Rosenqvist, Klemperer and Tritschler), the older communications on the subject are frequently of doubtful value in view of the faulty methods used in the earlier determinations of oxalic acid, and the neglect to take into account the oxalic acid present in the food.

Oxaluria, so far as we know at present, possesses no importance[2] as a cause of pathological phenomena ; its importance is purely extrinsic, and consists in the formation of the sediment and calculi[3] to which calcium oxalate may give rise.

Treatment.

Treatment of oxaluria is only applied with the object either of preventing the formation of concretions or of removing them.

Towards the accomplishment of this object two paths are open to us :

1. Diminution of the excretion of oxalic acid.
2. Increasing the solubility of calcium oxalate in the urine.

The first part of the problem requires the exclusion from the diet of articles containing oxalic acid (vegetables), or capable of producing it (gelatin, etc.), and, further, the artificial diminution of resorption of oxalic acid in the digestive tract, which can be attained by lowering the acidity.

To fulfil the second requirement it is in our power to increase the acidity of the urine (by meat diet), to increase the quantity of magnesium in the urine relatively to the calcium—according to Klemperer and Tritschler, by the choice of food poor in lime and rich in magnesia. Moreover, the attempt may be made to effect the solution of deposits by giving larger quantities of liquid.

[1] Numerous cases have been collected by Minkowski (21) and G. Toepfer (48).

[2] With regard to this, Minkowski (21) rightly points out that it is really only by accident that the rather unimportant excretion of oxalic acid has attracted such an enormous amount of interest. Its easy detection, and the characteristic appearance of its calcium salt under the microscope, have—especially in the early days when the urinary precipitates were examined with special care—enabled all those to co-operate in this field who had only just over the minimum chemical technique at their disposal. This accounts for the flood of researches on oxalic acid.

[3] The discovery of oxalate calculi is due to Wollaston (51) in 1797 ; he also discovered cystin calculi.

Tests for, and Determination of, Excreted Oxalic Acid.

These are effected by transforming the oxalic acid into its characteristic calcium salt; deposits are treated in the same way, and also examined under the microscope.

Two trustworthy methods[1] are known for the quantitative estimation of oxalic acid—those of Salkowski (11) and Autenrieth and Barth (13). In both the separation of the oxalic acid from the phosphoric acid and other urinary constituents depends on the solubility of oxalic acid in a mixtue of alcohol and ether. In Salkowski's method the urine is directly, or after previous concentration, acidified and extracted with ether. Autenrieth and Barth prefer to precipitate the oxalic acid as calcium oxalate first, and then to transfer it from an acid solution into ether. In both cases the oxalic acid which has been separated is again transformed into the calcium salt and weighed as CaO.[2]

LITERATURE.

1. Prout: Die Krankh. des Magens und der Harnorgane. 1843.
2. Buchheim u. Piorkowski: Uebergang einiger organ. Säuren in den Harn. A. p. H. **1.** 124. 1857.
3. Klemperer u. Tritschler: Über Herkunft und Löslichkeit der im Urin ausgesch. Oxalsäure. Z. M. **44.** 387. 1902.
4. Fürbringer: Zur Oxalsäureaussch. durch den Harn. D. Ar. M. **18.** 143. 1876.
5. Dunlop: Excret. of Oxalic Acid in Urine and its Bearing on Oxaluria. J. P. and B. **3.** 1896. P. 389.
6. Neubauer: Z. a. C. **8.** 521. 1869.
7. Fürbringer: Über einen mit hochgradiger Oxalurie, etc., komplizierten Fall von Diabetes. D. Ar. M. **16.** 494. 1875.
8. Rosin: Ueber die rationelle Behandlungsmeth. der Oxalurie. T. G. **1902.** Juli.
9. Schunck: P. R. **15.** 250. 1867; **16.** 140. 1868.
10. Neubauer: Z. a. C. **7.** 225. 1868.
11. Salkowski: Ueber die Bestim. der Oxalsäure und das Vorkommen von Oxalursäure im Harn. Z. p. C. **29.** 437. 1900.
12. Luzzatto: Zur Physiol. der Oxalsäure und Oxalursäure im Harn. Z. p. C. **37.** 225. 1903.
13. Autenrieth u. Barth: Ueber Vorkom. und Bestim. der Oxalsäure im Harn. Z. p. C. **35.** 327. 1902.
14. Cipollina: Ueber Oxalsäure im Organismus. B. k. W. **1901.** 544.
15. Esbach: L'oxalurie. Bu. g. t. **5.** 15. 1883.
16. Stradomsky: Die Beding. der Oxalsäurebild. im menschl. Organismus. Ar. p. A. **163.** 404. 1901
17. Pierallini: Ueber alimentäre Oxalurie. Ibid. **160.** 173. 1900.

[1] Of these two methods, Autenrieth and Barth's is the better. When the amount of oxalic acid in a urine is small, a large number of extractions with ether is required, and evaporation of such dilute solutions destroys some of the oxalic acid. Luzzatto, using Salkowski's method, extracted from nine to eighteen times with ether. On the other hand, it seems that with five extractions Autenrieth and Barth's method only yields about 95 per cent. of the oxalic acid. Working with Autenrieth and Barth's method we have obtained excellent results by using a form of apparatus for continuous extraction with ether. For a more recent method than Salkowski's, or Autenrieth and Barth's, see Albahary, *Compt. Rend.*, 1903, 136, pp. 1681, 1682.

[2] See Vol. I., p. 149.

18. Mohr u. Salomon: Unters. zur Physiol. und Path. der Oxalsäurebildung. D. Ar. M. **70.** 486. 1901.

19. Rosenqvist: Cit. in E. v. Leyden's Ernährungsther. 1904. P. 307.

20. Gaglio: Ueber die Unveränderlichkeit des Kohlenoxyds und der Oxalsäure im tier. Organismus. E. A. **22.** 233. 1887.

21. Minkowski: Oxalurie, in v. Leyden's Ernährungsther. **1904.** P. 307.

22. Mills: Ueber die Aussch. der Oxalsäure durch den Harn. Ar. p. A. **99.** 129. 1885.

23. Auerbach: Zur Kennt. der Oxydationsvorgänge im Tierkörper. Ar. p. A. **77.** 226. 1879.

24. Lüthje: Zur physiol. Bedeutung der Oxalsäure. Z. M. **35.** 271. 1898.

25. Lommel: Ueber die Herkunft der Oxalsäure im Harn. D. Ar. M. **63.** 599. 1899.

26. Kutscher u. Schenck: Zur Kenntnis der Oxalurie. Z. p. C. **43.** 337. 1904.

27. Fürth: Beitr. zur Kennt. des oxydat. Abbaues der Eiweisskörper. Be. P. P. **6.** 296. 1905.

28. Seemann: Ueber die Oxydation von Leim und Hühnereiweiss mit Calciumpermanganet. Z. p. C. **44.** 229. 1905.

29. Ranke: J. P. C. **56.** 15. 1852.

30. Pohl: Ueber den oxydat. Abbau der Fettkörper im tier. Organismus. E. A. **37.** 413. 1896.

31. Wiener: Ueber Zersetz. und Bild. der Harnsäure im Tierkörper. E. A. **42.** 379. 1899.

32. Wöhler u. Frerichs: Ann. der Chem. u. Pharmak. **65.** 344. 1848.

33. Gallois: Ueber Calciumoxalat im Harnsediment, etc. G. m. P. **1859.** Nr. 35.

34. Salkowski: Ueber die Bestimmung von Oxalsäure, etc., im Harn. Z. p. C. **29.** 437. 1900.

35. Salkowski: Beitr. zur Chem. des Harns. Ar. P. M. **2.** 358. 1869.

36. Eppinger: Ueber das Verhalten der Glyoxylsäure im Tierkörper. Be. P. P. **6.** 492. 1905.

37. Almagia: Zur Lehre vom Harnsäurestoffwechsel. Be. P. P. **7.** 472. 1906.

38. Schloss: Ueber den Nachweis und die physiol. Bedeut. der Glyoxylsäure. Diss. Strassb., **1906.**

39. Salkowski: Ueber Entstehung und Aussch. der Oxalsäure. B. k. W. **1900.** Nr. 21. 434.

40. Zopf: Oxalsäuregärung bei typischen Saccharomyceten. Ber. d. D. botan. Ges. **7.** 94. 1892.

41. Emmerling: Beitr. zur Kenntnis der Eiweissfäulnis. Ibid. **29.** 2721. 1895.

42. Mayer: Über Kohlehydratsäuren. Z. M. **47.** H. 1, 2. 1902.

43. Hildebrandt: Ueber eine exper. Stoffwechselabnormität. Z. p. C. **35.** 141. 1902.

44. Mayer: Ueber unvollkommene Zuckeroxydation im Organismus. D. m. W. **1901.** Nrs. 16, 17.

45. Baldwin: Ueber Oxalurie. J. E. M. **5.** 22. 1900.

46. Reale u. Boeri: Ueber die Bild. von Oxalsäure im Organismus bei Sauerstoffmangel. W. m. W. **1893.** Nr. 38.

47. Terray: Ueber den Einfl. des Sauerstoffgehaltes der Luft auf den Stoffwechsel. Ar. P. M. **65.** 393. 1895.

48. Toepfer: Oxalurie. W. K. **30.** H. 3. 1904.

49. Zickgraf: Die Oxydation des Leims mit Permanganaten. Z. p. C. **41.** 259. 1904.

50. Otori: Die Oxydation des Pseudomucins und Kaseïns mit Calciumpermanganat. Z. p. C. **43.** 86. 1904.

51. Wollaston: P. T. 1797.

52. Bakhoven: Over de afscheiding van oxaalzuur. Diss. Utrecht, **1902.**

CHAPTER XIII

PHOSPHATURIA

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Translated by W. H. Hurtley. D.Sc. (Lond.).

Like oxaluria, the anomaly which has received the indefinite designation of phosphaturia presents no uniform, nor even any well-defined, features.

By phosphaturia is understood the excretion of a turbid, frequently milky, urine, which, without the slightest ammoniacal decomposition, yields a more or less dense sediment. This deposit consists of the normal calcium and magnesium phosphates,[1] $Ca_3(PO_4)_2$, and $Mg_3(PO_4)_2$, frequently admixed with small quantities of the carbonates of the same metals. The urine issues from the bladder in the state referred to, and clears by sedimentation on merely standing.

This obvious condition of the urine, with its striking appearance, arrests in an unusual degree the attention of patients affected with it, and has given rise to a flood of papers on the subject quite out of proportion to its actual importance. In spite of this overwhelming abundance of literature, there is no unanimity whatever on the question as to whether or no phosphaturia is to be regarded as a definite anomaly.

Two errors have long prevailed, and prevail even now, with many medical men : firstly, the notion that the excretion of phosphates in solid form—*i.e.*, their appearance as a sediment in the urine—corresponds to an actual increase of these substances ; secondly, the view that this deposition is always a sign of a morbid process.

The deposition of insoluble phosphates comes about in two ways : (1) from a relative increase of alkalis ; (2) from a relative decrease of acids in the urine.

The phosphoric acid of normal urine is combined with alkalis, ammonia, lime, and magnesia. Whether the phosphates of the alkaline earths will be deposited in an insoluble state will depend on the absolute as well as on the relative quantities of the bases, on the reaction of the urine, on its content in free carbonic acid, and on other conditions which

[1] In the original these salts are referred to as basic calcium and magnesium phosphates. In this translation the following nomenclature has been employed :

$Ca(H_2PO_4)_2$ is called calcium diacid phosphate.
$CaHPO_4$ is called calcium monacid phosphate.
$Ca_3(PO_4)_2$ is called normal calcium phosphate.

Similarly for magnesium.

cannot at present be specified with certainty. In any case, the phenomenon is more complicated by far than is ordinarily assumed (1, 2).

That even a marked increase in the deposition of insoluble earthy phosphates allows of no conclusion being drawn as to the total amount of phosphoric acid in the urine follows at once from the well-known fact that in the filtrate from the deposited phosphates there are still present soluble phosphates, or phosphates which are deposited on heating.

A simple calculation, moreover, will show that lime and magnesia can be very largely increased without there being any lack of phosphoric acid to combine with them. The amount of P_2O_5 in the day's urine is, on an average, 2·0 to 2·5 grammes; in the same time 0·2 to 0·3 gramme MgO, and 0·15 to 0·5 gramme CaO are excreted—that is, taken together, the weight of the oxides of the alkaline earths is at the most one-third that of the P_2O_5. Now P_2O_5 is able to unite with just over four-fifths of its weight of magnesia and just under one and one-fifth times its weight of lime.

Clinicians distinguish, on practical grounds, the following forms of phosphaturia: (1) Physiological; (2) nervous; (3) sexual; and (4) juvenile. These types are not sharply differentiated from one another (3).

It is for the physiological chemist to ascertain whether different metabolic disturbances are at the bottom of these different forms of phosphaturia.

1. Physiological Phosphaturia.

A diet which is rich in alkaline carbonates, or one containing alkaline salts of vegetable acids, or alkaline albuminates—both of which yield alkaline carbonates on combustion in the body—leads to a diminution of the acidity of the urine. One action of the alkaline carbonates is, in fact, to transform a greater or smaller part of the diacid phosphates which exist in solution in normal urine into the insoluble monacid or into the insoluble normal phosphates, as the following equation will show :[1]

$$3Ca(H_2PO_4)_2 + 6Na_2CO_3 = Ca_3(PO_4)_2 + 4Na_3PO_4 + 6CO_2 + 6H_2O.$$

Of course, the absolute amount of phosphoric acid is not changed by this, or by any similar, action of alkalis; the ratio of dissolved to undissolved phosphoric acid only is changed, and, in fact, in favour of the latter at the expense of the former. Here there is no question of an increased formation of phosphoric acid; neither has such ever been proved in the other forms of phosphaturia. An increase of phosphoric acid ions could, indeed, only act by dissolving the normal salts—that is, by bringing about the precisely opposite effect to that which is actually observed.

[1] This equation could not be realized in practice. With these proportions a part of the calcium, at least, would be precipitated as carbonate, and another part probably as monacid phosphate. Further, normal calcium phosphate is decomposed by much water into basic calcium phosphate and the monacid phosphate, and normal sodium phosphate does not exist as such in dilute aqueous solution, but is hydrolyzed to caustic soda and the monacid phosphate. In short, the reaction between diacid calcium phosphate and sodium carbonate in the proportions indicated by the above equation and in dilute solution would be exceedingly complex.

As the transformations here mentioned appear solely from the influence of alkalis, Leo (4) has proposed the designation " alkalinuria " for this form of phosphaturia.

Individual differences exist in the facility with which this alkalinuria sets in, but with many perfectly healthy people it appears after partaking even in moderation of vegetables and alkaline mineral waters.

A diet specially rich in lime and magnesia may, in some circumstances, act in the same way as one containing alkali.

For example, an increase of calcium ions may have as a consequence a conversion of soluble diacid calcium phosphate into normal calcium phosphate.[1]

$$Ca(H_2PO_4)_2 + 2CaO = 2H_2O + Ca_3(PO_4)_2.$$

An increased alkalinity of the urine may be due to a decreased excretion of acids in the urine, as well as to an increased amount of alkali taken up by it. Such a condition ensues in a perfectly normal manner after any meal rich in protein, in consequence of the abundant secretion of hydrochloric acid during the process of digestion. Accordingly, there is observed a physiological " phosphaturia," or, perhaps more correctly, an anaciduria, not uncommonly from two to three hours after the time of the chief meal, more particularly if this is rich in protein. Anaciduria may also set in in other cases if the organism suffers loss of acid from other causes, as on continued washing out of the stomach, pernicious vomiting (*e.g.*, of pregnancy) [Quincke], in hyperhydrochloria, and in gastric hypersecretion [G. Klemperer (5)]. Maly has shown by experiment that changes in the secretion of the gastric juice are accompanied by corresponding changes in the acidity of the urine.

2. Nervous Phosphaturia.

The earliest medical books contain descriptions of this type. There is hardly a neurasthenic manifestation to which phosphaturia has not been assigned as a result, or, with change of fashion, as a cause. Now, when, through Pawlow's fundamental work, the possibility of every organ being affected by nervous influences rests on a firmer basis than ever, the existence of a secretion neurosis of the kidneys, and of a disturbance of their selective activity occasioned thereby, is beyond doubt. Since, as already stated, there cannot, even in this case, be any question of an absolute increase of phosphoric acid, it must be assumed that there is at the most a decrease in the acidity of the urine as a result of nervous influences. Changes in the production of hydrochloric acid in the stomach of the kind already mentioned may also be of nervous origin—that is to say, that here also the phosphaturia may be an alkalinuria or an anaciduria. But it must be confessed that no proof of change in the alkalescence of the blood, nor of an increased output of alkalis by the kidneys as a result of nervous influences, has yet been brought forward.

[1] This equation does not represent the action of calcium ions, but of calcium and hydroxyl ions, and the latter would be far more effective in precipitating calcium phosphate than would calcium ions.

In this neurasthenic variety of phosphaturia [Peyer (6)] must also be included the forms which have been described by the French, "the phosphatic diabetes or phosphaturia," and the *essentielle phosphaturie* of Teissier (7) and Ralfe (8), and the *phosphaturie terreuse des dyspeptiques* of Robin (9). In these forms, it is true, the authors—*e.g.*, Teissier (*loc. cit.*)—record the excretion of quantities of phosphoric acid far above the normal—12 to 29 grammes (!) per day; but the method employed is certainly not free from objection, and the description of the method of working is quite inadequate. A final verdict upon these cases, without exact metabolic experiments and an absolute control over the intake of phosphorus, calcium, and magnesium, is impossible.

3. Sexual Phosphaturia.

From the clinical, and probably also from the chemical, point of view this type bears a close relation to the preceding form. Phosphaturia has been described in association with the most varied affections of the genital organs. In part it is probably brought on by the special diet which is adhered to in these cases, and so is due to the increased alkalescence of the urine caused by the food. But, according to Minkowski (10), it must be regarded as quite within the region of possibility that in these, as in neurasthenic cases, we have to do with an excessive and overanxious attention directed to what is merely a harmless urinary anomaly.

4. Juvenile Phosphaturia.

While in the two last-mentioned forms the significance of phosphaturia is doubtful, it is otherwise with this variety. But even this type is by no means sharply differentiated, especially from the nervous phosphaturia; on the contrary, the phosphaturia is associated with the neuroses of childhood in many instances. Here the strict metabolic control recently introduced into pediatric investigations has been successful in proving the existence of a real anomaly in a number of cases.

Sendtner (11) was the first who found an increase in the excretion of calcium in this form of phosphaturia, and discussed the possibility of regarding the disturbed calcium metabolism as the cause of the phosphaturia. But the matter was only cleared up by the detailed investigations of Soetbeer (12).

By means of comparative experiments on two children of the same weight, one of whom was healthy, while the other, a child of six, was suffering from severe phosphaturia, Soetbeer established the fact that in the excretion of phosphoric acid itself, of nitrogen, and of salts, no difference existed, but there was a difference in the calcium content of the urines. The quantity of the latter (0·382 gramme) was markedly increased—indeed, to almost three times the amount (0·113 gramme) excreted by the normal child. If, in the normal case, the ratio $CaO : P_2O_5 = 1 : 12$ approximately, then it amounted in Soetbeer's case to about 1 : 4. The copious deposit in this case also was not due to any

increased excretion of phosphoric acid, but to an absolute increase of calcium oxide and a resulting utilization of phosphoric acid to neutralize it; the relative diminution of the H_2PO_4' ions had for its effect a transformation of soluble phosphate into the insoluble normal salt.

The question whence the excess of lime in urine was derived was answered by Soetbeer's demonstration of an almost equivalent diminution of the calcium excretion in the fæces; the lime absorbed from the food was excreted to a greater extent by the kidneys than in a normal case, and less by the large intestine—that is to say, there is no question of a yielding up of lime by the organism itself.

Cornelia de Lange (13), Soetbeer and Krieger (14), have shown similar conditions to prevail in other cases of phosphaturia—Soetbeer and Krieger also in the case of an adult—and Tobler (15) and Moll (16) confirmed the observations in other cases of phosphaturia in childhood. Thus we are dealing with a real anomaly which depends, presumably, on a disturbance in the secretion of the mucous membrance of the large intestine. Soetbeer refers this disturbance to colitis, and has suggested the name "calcaruria" for this form of the anomaly, which is suitable in so far as—corresponding to the nature of the metabolic disturbance—calcium carbonate does, in fact, share in the formation of the sediment.

Interesting as Soetbeer's results are, and great as is the advance in our knowledge of the whole subject which they represent, still, they are by no means competent to explain all cases of juvenile phosphaturia.[1] Earlier investigators [see Albu and Neuberg (3)] had emphasized the fact that the apportionment of the excretion of phosphoric acid and lime depends to a large extent on the food, especially on the ratio of the amount of vegetable food to the amount of animal food, and that the same conditions are of considerable importance for the question whether CaO and P_2O_5 are excreted by means of the kidney or the intestine. The well-known difference in the metabolism of phosphorus shown by the carnivora and herbivora exhibits the profound influence which, among other factors, the content of the food in CaO and P_2O_5 exercises on the processes of resorption of these mineral substances. Only by elaborate metabolism observations could be established the correctness of the view that inflammation of the intestinal mucous membrane robs it of its power of secreting calcium.

Langstein (17), in harmony with the considerations advanced by Albu and Neuberg, has recently reported some experiments which show that Soetbeer's cases only represent a single morbid aspect of the phenomenon of juvenile phosphaturia. Langstein has observed cases in which no coincidence existed between "calcaruria" and clinically demonstrable intestinal affections, and thus the reason of the increased amount of calcium phosphate in the urine of children still remains unexplained. Tobler (15) has also pronounced against the constancy and the importance of the abnormally high quotient of $CaO : P_2O_5$.

Finally, it must be supposed that other morbid conditions which are seemingly accompanied by disturbances of phosphorus and calcium metabolism, such as rickets, osteomalacia, functional disturbances of

[1] For the earlier literature, see Soetbeer (12).

the sexual organs, and of the thyroid, are also able to co-operate in bringing about phosphaturia.

Attempts to influence the symptoms of phosphaturia have met with little success in most cases, and in view of the insecurity of the foundation for them, might not in all cases have been capable of being theoretically justified.

Soetbeer's type of the juvenile form has proved itself the most amenable to treatment; limitation of the diet rich in lime (milk, eggs, fruit), and the substitution for of it a diet poor in lime (meat, pototoes, cereals), bring the calcaruria and its symptoms to vanishing-point in a short time.

In other cases of phosphaturia the attempt has been made to directly increase the acidity of the urine, partly by selection of the food, and partly by the administration of inorganic or appropriate organic acids [*cf.* Minkowski (10)].[1] However, such measures have yielded uncertain results, and have sometimes been wholly unsuccessful [*cf.* Soetbeer and Krieger (14)].

LITERATURE.

1. E. Salkowski: Ueber die Loslichkeitsverhältnisse des phosphorsauren Kalkes im Harn. Z. P. C. **7.** 119. 1882.
2. H. Malfatti: Warum trübt sich der Harn beim Kochen? Ein Beitrag zur Lehre von der Azidität des Harns. Be. P. P. **8.** 472. 1906.
3. A. Albu u. C. Neuberg: Physiologie und Pathologie des Mineralstoffwechsels. Berlin, 1906. Pp. 141-146.
4. H. Leo: Die Alkalinurie. D. Ar. M. **73.** 605. 1902.
5. G. Klemperer: Zur Behandlung der Phosphaturie. T. G. **1.** 351. 1899.
6. Peyer: Phosphaturie. Vo. s. V. **1889.** Nr. 336.
7. J. Teissier: Lyon médical. De la phosphaturie à forme diabétique. **19.** 307. 1875.
8. Ch. H. Ralfe: Phosphatic diabetes. L. **1887.** 1. 411, 462.
9. A. Robin: La phosphaturie terreuse des dyspeptiques. Bu. g. t. **140.** 915. 1900.
10. O. Minkowski: in E. v. Leyden's Handb. d. Ernährungstherapie. 2. Aufl. **1904.** p. 319.
11. J. Sendtner: Zur Phosphaturie. Mü. m. W. **1888.** 671. Nr. 40.
12. F. Soetbeer: Ueber Phosphaturie. Ja. K. **56.** 1. 1902.
13. C. de Lange: Zur Kasuistik der Phosphaturie im Kindesalter. Ja. K. **57.** 93. 1903.
14. E. Soetbeer u. H. Krieger: Ueber Phosphaturie. D. Ar. M. **72.** 553. 1902.
15. L. Tobler: Phosphaturie und Calcariurie. Ar. P. P. **52.** 116. 1905.
16. L. Moll: Beitrag zur Ernährungstherapie der mit Phosphaturie einhergehenden Neurosen im Kindesalter. P. W. **30.** Nr. 42. 1905.
17. L. Langstein: Zur Klinik der Phosphaturie. M. K. **1906.** 406. Nr. 16.

[1] The solvent action of citric acid on the calcium phosphates is remarkable. This acid does not merely act in virtue of the hydrogen ions which its solution contains, but the anion of citric acid appears to have a specific action, probably forming a soluble complex ion with the ions of phosphoric acid.

CHAPTER XIV

DRUGS AND POISONS: THEIR INFLUENCE ON METABOLISM

By OTTO LOEWI.

Translated by J. M. Fortescue-Brickdale, M.A., M.D.

The action of drugs and poisons depends on the chemical and physical changes which they produce on various parts of the organism, and may be recognised by a quantitative alteration in function. Changes frequently are simultaneously produced in the poison itself, but these will not be discussed, as the influence of metabolic processes on poisons does not come within the scope of this article.[1] Still less does it include such secondary disturbances of metabolism as are produced by the primary functional change. Such disturbances are the natural sequence of all poisons when employed in sufficient quantities, though they cannot always be detected by the methods at our disposal. Where recognisable changes occur, we have to determine whether they arise directly or indirectly—that is to say, whether they are produced by the direct influence of the poison on the vital processes of protoplasm itself, or whether the poison acts on some special organ, such as the nervous system, the blood, or the thyroid glands, and thus gives rise to metabolic or functional disturbances in other parts of the body. Poisons may thus be classified as protoplasmic (influencing metabolism directly) and selective (influencing metabolism indirectly); but this classification involves cross division, for many poisons are both protoplasmic and selective—for example, the halogen narcotics—and can be made to exhibit more of one or the other quality according to the method in which they are employed. Thus, it may not be concluded that any single substance does not indirectly affect metabolism merely because, like phosphorus, it is *par excellence* a protoplasmic poison. In fact, since the discovery of the fundamental importance of the thyroids on general metabolism, this possibility must always be kept in view. On the other hand, the fact that a poison affects an isolated unicellular organism does not necessarily show that in higher animals it acts as a general cellular poison; it is here that are manifested the wide differences which occur in cells, and in some way correspond to the functions they fulfil. For all these reasons a classification of poisons on these lines must be abandoned, and, indeed, in the present state of our know-

[1] For this reason metabolic changes due to the oxidation of alcohol are considered elsewhere (*cf.* Index).

ledge there is none which can be adopted without involving some cross division.

Owing to the special characters of the subject in hand, the arrangement of sections will differ considerably from that adopted in other portions of this work. Particular metabolic changes will only be considered in a limited manner; pharmacology as relating to the function of various organs (*e.g.*, secretion) will only be treated in so far as appears necessary for the comprehension of general metabolic processes. Drugs such as water, salts, alcohol, and iodides, which have already been dealt with (*cf.* Index), will be considered only in connection with those points which have no special place in the scheme of the other chapters.

Of modern summaries on the pharmacology of metabolism, the careful treatise of S. Weber ("Ergebnisse der Physiologie," iii., 1904) is the only one which has been found of value in the compilation of this section, owing to its numerous references to the literature.

I.—WATER AND NEUTRAL SALTS.

The cellular and humoral elements of the organism require a certain amount of water for the performance of their normal functions. The amount of water formed during the oxidation of the food is not sufficient, as is seen by the fact that death from starvation takes place more rapidly when water also is withheld. Water, therefore, must be added to food, but the minimum amount necessary cannot be accurately decided. It depends, among other things, on the nature of the food (amount of salts, extractives, etc.) and on the idiosyncrasy of the individual, which again partly depends on habit. Daily experience and the result of exact experiment show that the necessary minimum may be comparatively largely increased without any ill results, so that the sensation of thirst determines the amount taken as well as indicating the actual requirements of the organism.[1]

A.—NEUTRAL SALTS WITHOUT IONIC ACTION.

The result of adding neutral salts, especially sodium chloride, to the diet has been carefully studied by numerous observers. The experiments have been carried out chiefly on dogs, and it has been shown that the effect on protein metabolism varies according to the concentration in which the salt is given. Small amounts are without importance, as the organism is as unaffected, within certain limits, by variations in the intake of sodium chloride as in that of water; at any rate, this holds for protein metabolism, the only process which has hitherto been investigated. On the other hand, large amounts of sodium chloride produce definite

[1] For detailed account of the action of water and common salt, *vide* Vol. I. and Mineral Waters, Vol. III.

changes in the elimination of nitrogen ; this, again, varies according as the salt is given in such a concentration as to increase the elimination of water or not. In the first case the almost specific action of the salt is concealed by the results of loss of water ; the organism loses nitrogen. In the last case only are the results produced by salts *per se* quite evident ; here a trifling diminution in nitrogen excretion occurs. This has been recently shown for sodium chloride, and further investigations have proved that this is a general result of the action of all neutral salts (2, 3). Rost (4) has shown this in the case of sodium nitrate : when a loss of water was allowed to take place, a deficit of about 10 per cent. occurred in the nitrogenous balance-sheet. When, however, enough additional water was given to prevent loss by the organism, the administration of 1 grain per kilogramme of body-weight (or 12 grains to a dog weighing 12 kilogrammes) caused an economy of nitrogen to the extent of some 4 per cent. (5, 6, 7). This effect on nitrogen elimination is produced by all salts, not only the neutral and easily absorbed salts, but also by the alkaline ones which are absorbed with difficulty, such as sodium acetate, carbonate, sulphate, and phosphate. The explanation of this result is, however, very obscure. It is highly improbable that it arises from a retention of the end-products, as the phenomenon is most marked when no deficiency of water occurs.

Respiratory gaseous metabolism under the influence of neutral salts has hitherto only been observed after the introduction into the stomach of Glauber's salt, which is absorbed with difficulty. A method could thus be obtained for estimating the effect of gastric activity on the metabolic balance-sheet. Experiments by the Geppert-Zuntz method on six men who had taken 5 to 15 grammes of Glauber's salt dissolved in water showed sometimes a rise of 30 to 35 per cent. above the normal respiratory interchange when at rest, and sometimes under apparently the same conditions no alteration at all (8).

Hay has shown that the increased density of the blood resulting from increased elimination of water by the bowel is due to decreased absorption brought about by the presence of Glauber's salt (9). This was confirmed by Swiatecki (10), who was also able to demonstrate an increased alkalinity of the blood. The influence of one salt on the excretion of another will be dealt with later (*vide* Action of Alkalis).

The experiments of Loeb, which have shown how sensitive certain organs, especially heart and striped muscle, are to the slightest changes in the quality or quantity of the supply of so-called " neutral " salts, emphasize also how little light the gross determinations of the excretions can shed on the character of the finer metabolic processes.

Hitherto these methods have singularly failed to elucidate the mode of action of those salts whose ions undoubtedly have an obvious influence on general metabolism. Iodides and bromides fall naturally into this category.

Other salts, such as the chlorates, whose ions affect cellular processes, are considered later.

B.—IODIDES AND BROMIDES.

1. Iodides.

As the action of iodides is partially due to the iodine set free in the body, the effect of iodine in therapeutic doses should be identical with that of the iodides.

The activity of the salts of hydriodic acid, and of iodine itself, in producing the absorption of effusions and swellings from various causes, is only equalled by the poverty of the results of metabolism experiments in elucidating the rationale of their effect.

Magnus-Levy (11) has made very exact observations on the influence of potassium iodide and iodine on healthy and sick men without being able to show the smallest change in their intake when at rest; the doses were 3 to 10 grains of potassium iodide, and 4 to 10 drops of tincture of iodide daily, and the experiments lasted for weeks.

It is specially important to notice that iodine treatment failed in cases of myxœdema, whereas thyroidine produced increased metabolism, another proof, if such were needed, of the remarkably specific action of the thyroid compound of iodine.

In only one case (that of an emphysematous patient) was there any increased oxygen consumption under the influence of iodine; but this is not to be attributed to a specific action of the drug on metabolism, but must be explained entirely by the very marked reaction of the patient to treatment, which set up intense bronchial irritation and a tendency to pyrexia in the evening (*cf.* Magnus-Levy).

In syphilitics the CO_2 excretion is not altered by the action of iodides [Cederkreutz (12)]. Experiments on dogs by T. Bloch (13) showed similar results. On the other hand, Henrijean and Corin (15) found a rise in the respiratory quotient both in men (by the Geppert-Zuntz method) and in dogs. The inspired oxygen and expired carbon dioxide varied in their behaviour in the several experiments; at one time the oxygen intake remained unaltered, at another time it rose considerably, while on a third occasion it fell to a like degree. The amount of CO_2 output varied proportionately. As long as the cause of these irregularities remains unexplained the observations have no particular claim to our attention.

The protein metabolism is not affected appreciably by iodides in therapeutic doses, any more than is the respiratory interchange (11, 12, 14, 17). Some experiments give less clear results (15, 16, 18, 19, 20).

The significance of the so-called "iodine pyrexia"—a rise of temperature sometimes observed when iodine is given by other ways than the mouth—is doubtful (23).

2. Bromides.

Protein metabolism in men and animals is not appreciably influenced by bromide of potassium, even in large doses [10 grammes per diem (21),

46 grammes in ten days (22)]; but while the excretion of sulphates and nitrogen was unaltered, that of phosphorus fell remarkably.

	Day.							
	First.	Second.	Third.	Fourth.	Fifth.	Sixth.	Seventh.	Eighth.
	Gm.	Gm.	Gm.	Gm.	Gm.	Gm.	Gm.	Gm.
KBr	—	—	10	10	—	—	10	—
P_2O_5 in urine.. ..	0·889	0·825	0·680	0·638	0·734	0·832	0·699	0·723

The average P_2O_5 excretion on the days when no bromide was taken (1, 2, 6) was 0·849 gramme, on the bromide days 0·672 (decrease of 19 per cent.), and on the days succeeding the bromide (5, 8) 0·728 gramme (decrease of 13 per cent.). The cause of this peculiar phenomenon is obscure.

LITERATURE.

1. Magnus-Levy: This book. **1.** 1907.
2. Straub: Ueber den Einfl. des Kochsalzes auf die Eiweisszersetzung. Z. B. **37.** 527. 1899.
3. Magnus-Levy: l. c., No. 1.
4. Rost: Ueber den Einfl. des Natronsalpeters auf den Stoffw. des Hundes. A. k. G. **18.** 78. 1901.
5. Mayer: Ueber den Einfl. der Natronsalze auf den Eiweissumsatz im Tierkörper. Z. M. **3.** 82. 1881.
6. Salkowski u. Munk: Ueber die Bezieh. der Reaktion des Harns zu seinem Gehalt an Ammoniaksalzen. Ar. p. A. **71.** 500. 1877.
7. Rost: l. c., P. 98.
8. Loewy: Ueber den Einfl. der salin. Abführmittel auf den Gaswechsel des Menschen. Ar. P. M. **43.** 575. 1888.
9. Hay: Physiol. Action of Saline Cathartics. J. A. and P. **16.** 17. 1883-1884.
10. Swiatecki: Ueber die Alkaleszenz des durch Wirk. grosser Natrium sulfuricum-Gaben verdichteten Blutes. Z. p. C. **15.** 47. 1891.
11. Magnus-Levy: Untersuch. zur Schilddrüsenfrage. Z. M. **33.** 269. 1897. Ueber Myxödem. Ibid. **52.** 201. 1904.
12. Cederkreutz: Beitr. zur Kenntnis des Stickstoffw. in der Frühperiode der Syphilis nebst Untersuch. über die Einwirk. therap. Hg- und Jk-Gaben auf den Stoffw. des Menschen. Diss. Breslau, 1902.
13. Bloch: Einfluss von Jod, Thyrojodin und Thyraden auf den Stoffwechsel. Diss. Würzb., 1896.
14. von Böck: Ueber die Zersetz. des Eiweisses unter dem Einfluss von J und Hg. Z. B. **5.** 393. 1869.
15. Henrijean u. Corin: Über die Wirk. der Jodide. Ar. intern. de pharmacodyn. **2.**
16. Levi: Vergleichung der Einwirkung einiger Hg-Präparate und des Jodkaliums auf den Stoffw. und das Blut der Syphilitischen. Ma. **24.** 560. 1894.
17. Pagliari u. Rem Picci: Ueber den Einfl. des Jodkali auf den Stoffwechsel. Poliklin. **1895.** Ma. **1896.** 729.
18. Berg: Ueber die Wirk. der sog. Alterantien, insbesondere des Hg auf den Stoffwechsel. Diss. Rostock, 1881.
19. Fubini: Einfl. des Jodkaliums auf die Menge des im Harn ausgesch. Harnstoffes. Mo. U. **13.** 111. 1888.

20. Smirnow: Ueber den Einfl. von Jod in Verbindung mit Alkalim. auf die N-Aussch. Diss. Petersb. Ma. **1884.** 397.
21. Schultze: Ueber den Einfl. des Bromkalium auf den Stoffwech. Z. B. **19.** 301. 1883.
22. Chittenden and Culbert: Infl. of Potassium and Ammon. on Metab. Trans. Connecticut Acad. Arts and Sc. **7.** 1886.
23. Loewi: Pharmakol. des Wärmehaushalts. Er. Ph. III. **1.** 332. 1904.

II.—ACIDS.

When substances having acid properties circulate in the blood, an acid action is always present, and that not only when inorganic or unoxidizable organic acids [with the exception of CO_2 and evidently also hippuric acid (4, 7)], are ingested, but also acid salts (1), neutral salts of ammonia in so far as they are broken up in the organisms by fixed alkalis with the production of free acids (2), and finally organic bodies which, like protein, produce an acid residue on combustion (1, 2, 3), or are converted into unoxidizable inorganic acids (4). The organism, however, has no need to get its acid from outside; under certain circumstances it can manufacture acids from its own tissues, occasionally to such an extent as to produce severe intoxication. Such acid formation occurs, for instance, in starvation, in the course of infectious diseases, diabetes, and in certain toxic conditions. Among the latter must be classed, firstly, all those in which, owing to inadequate supply of acids or changes in the condition of the cells, oxidization is decreased, and secondly, a long series of intoxications produced by substances the action of which is still in certain cases but imperfectly understood, such as certain metals and emetin (5). The presence of these substances in the tissues is associated with a diminution in the amount of acid used up in the tissues consequent on changes in their oxidizing capacity. The entry of acid material into the blood liberates carbonic acid from its compounds. The CO_2 content in the blood therefore falls (1, 6, 7, 8), and the alkalinity is diminished (4, 6, 7, 9). The expulsion of CO_2 from the blood by stronger acids appears to be the actual cause of the fall in CO_2 excretion, particularly in acid intoxication; increased respiratory activity, decreased formation of CO_2, or decreased power in the blood to combine with CO_2, appear usually to play a subordinate part (5, 7, 10, 11). The amount of the fall varies in degree in different classes of animals: in herbivora it is greater than in carnivora and omnivora (7); the former succumb to acid intoxication much sooner than the latter. The cause of this difference lies in the different ways in which the animals neutralize the acid, and so protect themselves against it. This can be seen in the manner in which the quantity of alkali in the urine alters under the influence of acids; the salt which is formed for neutralization purposes is rapidly excreted in the urine, as it forms no part of the constant composition of the tissues (6, 7). Carnivora, including man, lose no fixed alkali (12), or only a negligible amount (4, 13, 14, 15, 24).[1] Often, on the other hand, there is a certain

[1] For particulars as to the behaviour of the fixed bases in diabetic acidosis in man *cf.* Diabetes, p. 613.

alteration in the excretion of the bases ; under the influence of acids the excretion of potassium rises, while that of sodium falls (4, 20). Carnivora, as Salkowski (23) suggested and Walter (7) showed conclusively, neutralize acids mainly by ammonia formation, which is withdrawn from the urea synthesis. The amount of urea, therefore, drops to a corresponding degree (15). This has been shown for men by Coranda and others (14 to 17). Birds protect themselves similarly (2, 18, 19). That the increased ammonia excretion is actually due to the necessity for acid neutralization, and not to some primary disturbance in the synthesis of urea, is shown by the fact that it corresponds almost exactly to the amount required (1, 4, 7, 20).[1] Further support for this view, which was from the first very generally accepted, is derived from the fact, first brought forward by Salkowski and Munk (21), and subsequently confirmed by others, that it is possible by the exhibition of fixed alkalis to bring back the ammonia excretion to normal. The power of neutralization possessed by ammonia is extensive but not unlimited, or else there would be no acid intoxication in carnivora (1, 22). In herbivora the excretion of bases during acid intoxication is very different. In contrast to what obtains in carnivora, this excretion is materially raised (23), and the animal suffers, as a certain constant of alkali is necessary for normal metabolism. The amount of fixed alkali which can be utilized in the tissue fluids is very limited—much less, indeed, than the amount of available ammonia in the carnivora. This has long been recognised as a fundamental difference between the two classes of animals. But recently it has been shown experimentally that herbivora also have the power of neutralizing acids with ammonia (26). On their ordinary diet this decreases to such an extent that it ultimately disappears (27). The cause of this appears to lie partly in the special character of the diet, and the modifications of function in certain organs (especially, perhaps, the pancreas) which are thereby induced (26). This is shown to be the process according to the latest experimental data, by which it appears that it is possible to increase NH_3 excretion enormously in rabbits suffering from an acid intoxication by simultaneously feeding them with amino-acids without preventing the increased excretion of fixed alkalis. The supply of amino-acids always produced such a condition of protection that the animals were able to survive the usually fatal amount of acid, and the CO_2 content of their blood did not fall below normal. The same thing occurred when rabbits were fed for a long time with blood-serum. It cannot at present be definitely decided how far the animals become accustomed to the new conditions, or what part may be played by the pancreas in the formation of ammonia. The experiments seem to show that we have the power to modify the difference in acid neutralization between carnivora and herbivora. Some of the results have not been confirmed (30).

As the normal oxidation processes in the body occur in alkaline solutions, it is evident that decrease in alkalinity will produce severe disturbances of general metabolism. On this point it is remarkable

[1] In Gathgen's experiments the NH_3 excretion still remained high after the acidity had returned to normal ; the fixed alkalis were correspondingly diminished.

that only one research has been made ; this one, however, is very accurate, and deals with the influence of acid intoxication on the respiratory exchange in rabbits [Chvostek (10)]. There was a decided decrease in oxygen intake and carbonic acid output, as had previously been shown. The following table gives the results. Rabbits were used, and 0·9 gramme of a 0·2 to 0·3 per cent. solution of HCl per kilogramme body-weight was given by the mouth.

Number of Experiment.	*Weight.*	*O_2 Intake per Kg. per Hour.*	*CO_2 Output per Kg. per Hour.*	*Respiratory Quotient.*
	Kg.	c.c.	c.c.	
1	2·6	Before HCl : 782·0	576·5	0·737
		After HCl : 641·1	446·2	0·695
2	3·6	Before HCl : 645·2	547·1	0·847
		,, ,, 642·2	447·9	0·697
		After HCl : 576·2	423·6	0·733
		,, ,, 522·3	369·5	0·709
3	2·1	Before HCl : 679·6	663·7	0·975
		After HCl : 576·6	502·5	0·875
4	2·5	Before HCl : 883·1	528·2	0·597
		,, ,, 704·8	445·3	0·631
		After HCl : 579·7	479·1	0·923
		,, ,, 412·4	318·1	0·771

It cannot be said with certainty to what this decrease of oxidizing power is to be attributed. Deficiency of oxygen as a cause can be excluded, as the supply of oxygen from the blood to the tissues was certainly sufficient. Analyses of the blood-gases show that there is no decrease in O_2 in the blood during acid intoxication (7). Nor is the power of the blood to part with O_2 diminished (11). The motor functions of the animals were augmented, owing to the increase in the rate and depth of respiration and the consequent extra muscular exertion involved. The lowered oxidation must therefore be due to the decrease in metabolic activity consequent on changes in the condition of the tissues arising from carbonic acid poisoning or direct chemical alterations brought about by relative deficiency of alkali. Both might, *a priori*, decrease the oxidative activity. Support is given to this view by the fact that a horse suffering from acid intoxication oxidized less phenol than normal [Munk (28)].

Specific changes in protein metabolism have not been distinctly demonstrated. Very accurate experiments have failed, as a rule, to show any changes in the protein metabolism of dogs (11, 20). In men Coranda and Dunlop found (15, 16) a slight increase in the nitrogen elimination, but this is probably not due to the acid itself, but to the loss of water. Owing to the ingestion of acid more salt is formed; and in both these cases the diuresis exceeded the intake of water.

Glycosuria has been observed to follow the introduction of acids into the stomach and into veins. Pavy (31) and E. Külz (32) injected phosphoric acid intravenously into rabbits ; after two hours the latter found sugar and albumin in the urine. Concentrated lactic acid injected

into the stomach caused the appearance of sugar in thirty-six hours (33), and even more dilute acid occasionally produces it before the urine contains albumin. Five grammes of a 5 per cent. solution of hydrochloric acid introduced into the stomach of a dog was followed by glycosuria (34), and sugar (glycuronic acid) is said to have appeared in the urine of a man the subject of sulphuric acid poisoning (35).

Certain cases confirm Naunyn's view (29) that the occurrence of glycosuria is very unusual; at all events, the conditions which determine it are very obscure. Most of the positive observations refer to the injection of acids in a form sufficiently concentrated to produce other severe disturbances. It cannot, therefore, be determined whether this is a specific anomaly in cases of acid intoxication. It may be said in favour of this view, as will be seen in intoxications to be described later, that where, as in this case, there is a decrease in the oxidative capacity of the cells, sugar is found, though not frequently. It would be significant if glycosuria appeared after the administration of lactic acid.

LITERATURE.

1. Auerbach: Ueber die Säurewirk. der Fleischnahrung. Ar. p. A. **98.** 512. 1884.—Kunkel: Handb. der Toxikologie. Jena. **1.** 294. 1899.—Spiro: Beitr. zur Lehre von der Säurevergift. bei Hund und Kaninchen. Be. P. P. **1.** 269. 1901.

2. Feder: Ueber die Aussch. des Salmiaks im Harn. Z. B. **13.** 256. 1877; **14.** 163. 1878.—Feder u. Voit: Zur Harnstoffbild. aus pflanzensaurem Ammoniaksalz. Z. B. **16.** 77. 1880.—von Knierim: Beitr. zur Kennt. der Bild. des Harnstoffs im tier. Organismus. Z. B. **10.** 263. 1874.—Salkowski: Ueber den Vorgang der Harnstoffbild. im Tierkörper und den Einfl. der Ammoniaksalze auf denselben. Z. p. C. **1.** 1. 1877.—Salkowski: Bemerk. über die Wirk. der anorganis. Säuren und den Fleischnahrung. Ar. p. A. **76.** 368. 1879.—Pohl u. Münzer: Ueber das Verhält. der subakuten Salmiakvergift. zur Säurevergiftung. E. A. **43.** 28. 1901.

3. Hofmann: Ueber den Uebergang von freien Säuren durch das alkal. Blut in den Harn. Z. B. **7.** 338. 1871.

4. Jolin: Ueber die Einwirk. neutraler, säurebildender Stoffe auf die Alkaliaussch. der Fleischfresser. Sk. Ar. P. **1.** 442. 1889.

5. Meyer: Über die Alkaleszenz des Blutes. E. A. **17.** 304. 1883.

6. Kraus: Ueber die Alkales. des Blutes durch Zerfall der roten Blutkörperchen. E. A. **26.** 186. 1889.

7. Walter: Ueber die Wirk. der Säuren auf den tier. Organismus. E. A. **7.** 148. 1877.—Jaquet: Ueber die Wirk. mässiger Säurezufuhr auf Kohlensäuremenge, Kohlensäurespannung und Alkales. des Blutes. E. A. **30.** 311. 1892.

8. Minkowski: Ueber den CO_2-Gehalt des Blutes bei Diab. mellitus. Mit. K. **1888.**—Kraus: Ueber die Alkaleszenz des Blutes bei Krankheiten. Z. H. **10.** 106. 1889.

9. Freudberg: Ueber den Einfl. von Säuren und Alkalien auf die Alkaleszenz des Blutes. Ar. p. A. **125.** 566. 1891.

10. Chvostek: Der oxydative Stoffw. bei Säureintoxikation. C. i. M. **14.** 329. 1893.

11. Loewy u. Münzer: Beitr. zur Lehre von der exper. Säurevergiftung. D. A. **1901.** 81, 174.

12. Gäthgens: Zur Frage der Aussch. freier Säuren durch den Harn. C. m. W. **1872.** 838.

13. Kurtz: Ueber die Entzieh. von Alkalien aus Tierkörper. Diss. Dorpat, 1874. C. m. W. **1874.** 569.

14. Keller: Ueber den Einfl. anorgan. Säuren auf den Stoffw. des Säuglings. C. a. P. **8.** 23. 1898.

15. Dunlop: Action of Large Doses of Dilute Mineral Acids on Metabolism. J. P. **20.** 82. 1896.
16. Coranda: Ueber das Verhalten des Ammoniaks im menschl. Organismus. E. A. **12.** 76. 1880.
17. Hallervorden: Ueber das Verhalten des Ammon. im Organis. und seine Beziehung zur Harnstoffbild. E. A. **10.** 125. 1878.
18. Milroy: Acid Poisoning in Birds. J. P. **27.** XII. 1901.
19. Kowalewsky u. Salaskin: Ueber den Ammoniak- und Milchsäuregeh. im Blute. Z. p. C. **35.** 552. 1902.
20. Gäthgens: Ueber Ammoniakausscheidung. Z. p. C. **4.** 35. 1880.
21. Salkowski u. Munk: Ueber die Beziehungen der Reaktion des Harns zu seinem Gehalt an Ammoniaksalzen. Ar. p. A. **71.** 500. 1877.
22. Magnus-Levy: Die Oxybuttersäure und ihre Beziehungen zum Coma diabet. E. A. **42.** 149. 1899.
23. Salkowski: Ueber die Möglichkeit der Alkalientziehung am lebenden Tiere. Ar. p. A. **58.** 1. 1873.
24. Limbeck: Beitr. zur Lehre von der Säurevergiftung. Z. M. **34.** 419. 1898.—Landau: Exper. Unters. zur Blutalkaleszenz. E. A. **52.** 271. 1905.
25. Winterberg: Zur Theorie der Säurevergiftung. Z. p. C. **25.** 205. 1898.
26. Eppinger: Beitr. zur Lehre von der Säurevergiftung. W. k. W. **1906.** Nr. 5.
27. Kettner: Ueber Fütterungsvers. mit Chondroitinschwefelsäure. E. A. **47.** 178. 1902.
28. Munk: Ueber die Oxydation des Phenols beim Pferde. D. A. **1881.** 460.
29. Naunyn: Der Diabetes mellitus. **1898.** 25.
30. Pohl u. Münzer: Ueber Entgift. von Mineralsäuren durch Aminosäuren und Harnstoff. C. P. **1906.** 232.
31. F. W. Pavy: Diabetes mellitus. 1869.
32. Külz: Beitr. zur Lehre vom künstl. Diabetes. Ar. P. M. **24.** 103. 1881.
33. Goltz: Melliturie nach Milchsäureinjektion. C. m. W. **1867.** 45.
34. Naunyn: D. A. **1868.** 413.
35. Frerichs: Ü. den Diabetes. **1884.** 30.

III.—ALKALIS.

It is as easy to withdraw alkalis from the body as it is difficult (at any rate, for any length of time) to maintain an excess of them. Naturally, no measures can be taken against the first eventuality, but it is easy to prevent an excess of alkalinity by increasing excretory activity. Any excess is got rid of by the exercise which is necessary to preserve the activities of the body undisturbed and its proper composition constant. It is no wonder, then, that the specific effect produced by the exhibition of alkalis in those cases in which previously no deficiency existed is much less marked than, *a priori*, we might be inclined to expect in view of their powerful action in increasing oxidation processes *in vitro*.

A.—THE ALKALINITY OF BLOOD.

The alkalinity of the blood can only be slightly and temporarily increased. The blood from the carotid of rabbits to which sodium carbonate had been administered for several days previously showed

twelve hours after the last dose a percentage of 26·12 to 26·5 by volume of CO_2, as against 23·77 to 27·72 normal, and usually no further alteration (1). Half an hour to an hour after the exhibition of large doses of soda there was always a rise to from 32·16 to 37·91 per cent. In fowls the rise in alkalinity was not maintained for any greater length of time (2), and no marked effect was produced in man (3).

As alkalis, in order to produce any action, must be given in large doses—the intensity of their action being directly proportional to the number of active hydroxyl ions—it is clear that it is not a matter of the action of alkalis pure and simple, but of their salts ; in most cases, however, it is very difficult to distinguish between the two, and to this we must attribute in great part the obscurity which surrounds the influence of alkalis on metabolism. The researches on the subject, though numerous, have often been somewhat one-sided.

B.—GENERAL METABOLISM.

In spite of the frequent practical use of alkalis in the form of mineral waters, their influence on general metabolism has seldom been the subject of experiment, and the published results do not go very far towards producing clear ideas on the subject. In man, some hours after the ingestion of 5 grammes of sodium carbonate there was an alteration in the gaseous exchange [Geppert-Zuntz method (4)]. Experiments on diabetics yielded no definite conclusions (5). Conclusions can only be very cautiously drawn from animal experiments, as movements and altered respiration may influence the results ; those in which these are excluded, however, are of interest. In rabbits under artificial respiration through a tracheotomy tube (6) there was increased consumption of oxygen and excretion of carbon dioxide. In spite of the somewhat abnormal circumstances in which the animals were placed, these experiments have a certain value ; the gaseous metabolism has diminished when acids, instead of alkalis, were exhibited under similar conditions (7). A newer experiment on a bitch which had been splayed is of more significance (8) ; the gaseous metabolism was increased 30 per cent. by the administration of very small doses of alkali—namely, 3 grammes of sodium carbonate twice daily. This increase continued after the soda had been discontinued, and then gradually fell to the normal value. The detailed report is not yet published. These few experiments seem to show that probably the influence on metabolism is marked and constant, and the last-quoted research shows that it is probably the action of the alkali, and not that of the salt, owing to the smallness of the dose. The increased metabolism is, moreover, in accord with the well-established action of mineral waters in practice in reducing the amount of fat. Although sceptical observers may ascribe the greater part of these results to the simultaneous diminution in diet, it does not appear at present to have been proved, at any rate, that this is the only factor in reducing the amount of fat ; the influence, too, of purgative salts

must not be over-rated, as the absorption of food would only usually be reduced in this manner at the beginning of the treatment. The following observations are also of interest in this connection (9); they extended over a considerable period, the diet remaining constant, and analyses were made of the ingesta and excreta: During the administration of large doses of alkalis (sodium bicarbonate and citrate) a considerable loss of weight occurred which, from the condition of the experiment, could certainly not have been due to loss of protein; the loss of water could not be absolutely excluded as a causal agent, as the amount of water excreted by the lungs was not estimated. A comparison, however, of the amount of water taken in with the amounts lost by the urine and fæces renders this supposition improbable, and it is at any rate likely that the loss of weight was partly due to loss of body-fat. Further support is given to this view by the result of investigations with borax (10, 11). Under the circumstances, it seems necessary that experiments should be undertaken on new lines to determine the influence of alkalis on general metabolism.

C.—PROTEIN METABOLISM.

Though so few researches have been made on the influence of alkalis on gaseous interchange, it is almost impossible to review all the work on the changes occurring in protein metabolism. One conclusion to be gathered from this is that no universally accepted results have as yet been obtained. In fact, the widely divergent figures seem to render the thought of such a thing ludicrously impossible. First of all, we may leave severely alone all the work, very useful in its time, which does not now fully come up to the standard of modern requirements in a metabolism experiment. In some the nitrogen balance was not calculated (12, 13); in others, during the experiment, severe digestive disturbances occurred (14), or the persons experimented on were diabetics (15), or only urea was estimated, and that in a way that, on calculation, gave an excretion of 2 to 5 grammes of nitrogen daily in men (16). In some of the following experiments the increased output of water interfered with the value of the results; but as we know the effect of this factor, it can be allowed for in the conclusions. The remaining references are given under 17, 25.

1. The Action of Small Amounts of Alkali.

(*a*) *In Man.*

Two to 6 grammes of sodium bicarbonate have no recognisable influence on protein metabolism (17, 18, 21, 22), taking the period during which alkali is given and the subsequent period together. This last is a necessary precaution, as the diminution in excretion which occurs in the former is, as a rule, compensated in the latter period. Larger doses of calcium carbonate, of which only a small portion can have been

absorbed, gave rise to no more effect on nitrogenous excretion (24). It must, however, be noted that the alkaline action of calcium salts is much greater than might be supposed from the amount which is excreted in the urine, because the calcium neutralizes the acids in the gastro-intestinal canal; the alkalis, therefore, in the intestinal and pancreatic secretions, and in the food, are no longer required for this purpose, and can be utilized to keep up the alkalinity of the blood. This holds true for all alkalis, even when they are neutralized in the stomach; less alkali, from the intestinal juice or from the food, is neutralized by the gastric and intestinal acids. We must therefore conclude that all alkalis, even those which are only absorbed to a slight degree, can, if given in sufficient quantity, produce an alkaline or nearly alkaline reaction in the urine.

(*b*) *In Dogs.*

Two to 3 grammes of sodium carbonate, or 5 to 10 grammes of calcium carbonate, had no influence on dogs (26), and the same was observed with 3·5 grammes of sodium acetate (25).

2. The Action of Larger Amounts of Alkali.

(*a*) *In Man.*

Amounts varying from 20 to 40 grammes of sodium acetate, bicarbonate, and citrate, have been given (19 to 23) with varying results. In some cases there was no alteration in the nitrogen elimination; in others the amount, which had been constant, became, under the influence of alkalis, very inconstant, and showed great variations. The variation was of two kinds: either the nitrogen during the following day was retained, and in the succeeding period gave rise to a corresponding increase in the urine (19 to 21), or from the beginning there was a sudden rise in the nitrogen excretion followed by a fall (23). In no case, however, did the average show any difference when compared with a normal period.

(*b*) *In Dogs.*

Doses of 7 grammes daily of sodium carbonate (dry salt) produced an increase in nitrogen excretion (25); the cause was most probably withdrawal of water—at any rate, diuresis was present, and the amount of water in the urine exceeded that taken with food. On the other hand, 7 grammes of sodium acetate and phosphate cause a noticeable fall in nitrogen elimination without any subsequent rise to correspond. Moreover, in this case also there was diuresis. The cause of this fall cannot be determined with certainty, but there are two possible explanations: it is known that the exhibition of moderate amounts of alkali produce a decreased nitrogenous waste; in this experiment it might have exceeded the increase in nitrogenous waste produced by the increased elimination of water. It seems more probable, however, that under the influence

of the salt the absorption of nitrogen was diminished—a view, however, which, in the absence of an analysis of the fæces, can neither be proved nor controverted. One dog under the influence of 13 grammes of sodium acetate showed no change in the nitrogen excretion (20); another with 10 grammes showed a very slight rise (27).

These observations show, on the whole, that alkalis have no specific effect on the amount of protein metabolism. The cause of the daily or periodic variations, so often observed, is obscure. They remind us of the similar symptoms which occur in the course of nephritis and gout, and occasionally also are accidentally observed in apparently healthy individuals (28).

D.—CARBOHYDRATE METABOLISM.

The alkalis, especially in the form of mineral waters, have for long been regarded as remedies for diabetes. Critical researches in hospitals have furnished no ground for this view (29), while experiments on the influence of alkalis on glycogen formation in dogs (30), fowls (31, 32), and rabbits (33), have given no results of any value. From the majority of the experiments an indulgent observer might draw some support for the idea that alkalis exert some restraining influence on the glycogenic function. In this connection, perhaps, the statement that sodium carbonate retards the action of diastase on glycogen is of some interest (34).

E.—CHANGES IN THE COMPOSITION OF THE URINE.

1. Alkalinity of the Urine.

The amount of urine is increased by large doses of alkalis for the same reason as by the exhibition of neutral salts. In both cases, moreover, the alkalinity is increased, so that there is a further rise in amount owing to the passage of alkalis with the urine. This never, however, takes place to such an extent that the urine will turn red litmus paper blue, but the hydrogen disodium phosphate is always increased, while the dihydrogen sodium phosphate is diminished.

This increase in alkalinity has a favourable influence on the solution of uric acid concretions, and prevents precipitates from forming (24, 36 to 39); hence alkalis are important agencies in the treatment of the corresponding pathological conditions (40). Calcium carbonate is specially suitable for this purpose, and has recently been extensively employed (40); this substance decreases the acidity of the urine more powerfully than the soluble alkalis, owing to the fact that it forms more insoluble compounds with phosphoric acid in the intestine, and thus checks its absorption. In the urine less phosphates and less dihydrogen salts appear, so that the acidity is reduced without the fall being sufficient to produce an alkaline reaction—at any rate, in man. An alkaline reaction is inadvisable, both on account of the risk of precipitating the phosphates and on account of its favouring bacterial growth.

2. Uric Acid.

The reputation so long enjoyed by the alkalis of being the sovereign remedy for gout—according to Pliny gouty Romans were ordered powdered oyster-shells (58)—has led to numerous experiments on the influence of alkalis on the excretion of uric acid. Experiments carried out on healthy persons by methods which are quite reliable show that there is no appreciable effect (24, 39, 41 to 44, 50 to 52). The slight and temporary decrease in uric acid excretion noted in two cases is doubtless to be explained by the presence of diarrhœa due to the exhibition of alkalis (20, 49); in both the total nitrogen excretion in the urine fell in almost the same ratio as the uric acid. For instance :

	Nitrogen.	*Uric Acid.*	$\frac{\textit{Uric Acid}}{\textit{Nitrogen.}}$
	Gm.	Gm.	
Previous period	26·6	0·82	1 : 32·3
Period with 145 grammes sodium acetate ..	24·9	0·69	1 : 36·0
Subsequent period	30·0	0·82	1 : 36·8

In experiments by His (42) on gouty patients the uric acid decreased to such an extent that it did not seem probable that such a change could be due to the alkalis alone (46, 59, 60). Hence the therapeutic value of the alkalis in gout, so far as it exists, must be attributed to some other action. It is a remarkable fact that the compounds of uric acid with organic bases such as lysidin and piperazin, which are easily soluble in water, are almost insoluble in physiological salt solution or blood-serum ; their effect on the uric acid excretion is variable (61 to 64, 86).

3. Ammonia.

The excretion of ammonia has been reduced in all the experiments hitherto described, both in normal individuals, and especially as a result of the increased excretion in acidosis (9, 21, 24, 53 to 55, 57, 65) ; but it cannot be completely excluded from the urine.

4. Sulphur.

The total sulphur excretion is not affected by the administration of alkalis—a fact which explains itself, considering the small effect produced on protein metabolism (17, 19, 66) ; in dogs a slight increase has been observed (35). On the other hand, the proportion between oxidized and neutral sulphur is remarkably altered in favour of the latter. Although opposite results have been obtained, these have been after more occasional observations which were not so conclusive as those first mentioned (43), as there was always a longer interval between the estimations, which were all made on the same dog.

No accurate conclusions can be drawn from the increase in neutral sulphur. Our knowledge of the conditions which determine the excretion of sulphur is not sufficiently wide to allow of our drawing any inference as to a diminution in oxidizing power from an observation such as this. The same reason does not permit our inclusion of an observation of Auerbach's (56), which shows that under the influence of alkalis a dog formed more phenol from benzol than without them. We have no right to quote this in support of other oxidations, as very different chemical processes underlie the various oxidation processes of the animal body.

5. Ethereal Sulphates.

The influence of alkalis on the excretion of ethereal sulphates has frequently been investigated, as it was hoped that some information could by this means be gained as to the value of the gastric hydrochloric acid as an intestinal disinfectant. In those suffering from hyperacidity (76, 77), and those under treatment with acids (78, 79), there was a decrease, but in those with subacidity there was an increase in the ethereal sulphates of the urine. In the same way it is said that the exhibition of alkalis is usually followed by an increased excretion of aromatic sulphates (9, 47, 48). On the other hand, von Noorden (45) and others (80 to 83) found no increase in cases of acidity, apepsia gastrica, and total resection of the stomach, and others observed no changes even after the administration of alkalis. From this we may conclude, as is very generally believed at the present time (84), that the gastric hydrochloric acid produces no special effect on intestinal asepsis. Hence the neutralizing power of alkalis is also unimportant (85).

6. Oxybutyric Acid.

The excretion of oxybutyric acid in diabetes is considerably increased (65), being due, as Magnus-Levy supposes, to increased formation rather than excretion of the acid, which is set free from some protein combination.

7. Fixed Alkalis.

The disturbances now to be described are the result of the administration, not only of alkalis, but also of neutral salts. They are grouped together because alkalis were used in most of the investigations. It must, too, be noted that the action of the salts of vegetable and fatty acids, which will be dealt with in the following pages, resembles that of the alkaline salts (viz., carbonates), into which they are converted after introduction into the body.

Bunge showed that, after taking potassium salts (citrate, phosphate, or chloride), the organism loses sodium in the form of common salt, and hence he concluded that the organism required common salt when the diet contained much potassium. He suggested two possible causes

for this loss of common salt : either the potassium combines with the sodium salts in the blood, thus forming abnormal combinations which are useless to the organism and are excreted, or the potassium salts " stimulate " the excretion of sodium salts mechanically. As to how the " washing out " is accomplished, we cannot at present form any idea.

In order to determine which of these two possibilities took place in reality, Bunge tried the effect of a sodium salt (citrate). For if the increased sodium excretion is always the result of a " washing out " process, sodium salts taken into the body should produce increased sodium excretion—in other words, sodium should expel sodium from the organism as well as potassium. The result of this experiment was that, though there was an increased excretion of potassium, there was no increase of chlorine ; hence it was certain that no excess output of NaCl could occur. But this important research is not, in our opinion, entirely conclusive. Indeed, Bunge himself considers it " not quite clear." For he conducted the experiment immediately after the one with potassium which we have described, by which the organism had lost so much sodium chloride, and was thus so poor in that salt at the beginning of the sodium experiment that, although he took about 2 grammes of common salt per diem, the urine only contained about half that amount. Thus, want of chlorides cannot be excluded as a cause of the failure to produce increased chlorine excretion.

A dog fed with a diet poor in common salt, when treated with KCl, was found, on the contrary, to excrete less and not more sodium in the urine (67) ; and likewise another dog, which was given sodium immediately after having been dosed with sulphuric acid, retained potassium phosphate, and excreted slightly less rather than more sodium. Thus it was concluded that the amount of sodium was an indication of the degree to which the sodium was reduced (68). Bunge comes to the following conclusions : " Of the two explanations which we have suggested for the increased excretion of sodium and chlorine after the exhibition of potassium, the experiments quoted do not support the last-mentioned—viz., that it is a mechanical process depending on increased diffusion and filtration. Against it is the fact that sodium citrate does not increase the excretion of chlorine, and the facts that sodium salts increase the excretion of potassium, and those of potassium the sodium, are much better explained on the former supposition—viz., that of a chemical interaction." If, owing to legitimate doubts as to the value of these experiments, we are not convinced that chemical interaction alone is the cause of the increased sodium excretion, though doubtless it is so to a certain extent, we shall find other experiments which can only be explained on the assumption of a further factor acting in concert with the chemical one in producing this result.

It has already been shown that in dogs sodium phosphate (69) or acetate cause a loss of sodium and potassium (69). Kozerski found that the ingestion of sodium citrate leads to an increased output of chlorides, and that not only more potassium, but more sodium, is excreted than is ingested. There was so little diuresis that it is highly improbable that this alone could cause the increased excretion of bases ; 59 c.c. of water

was passed in excess of the intake. The following considerations show how important this experiment is in deciding the question in hand: During the first sodium period the excretion of chlorine exceeded that of the previous period (after the loss of the excess of chlorine ingested) by 4·0991 grammes per diem, whereas for sodium (equally after the loss of the excess of sodium ingested) the figure was 0·4412 gramme per diem, and for potassium 0·4184 gramme.

In the period immediately following, with a still greater intake of sodium, the average daily excess of output over intake was 3·9115 grammes Na_2O. This great increase of sodium excretion after sodium ingestion is clearly not caused by chemical interaction, and shows that a mere process of this sort cannot explain the changes in alkali excretion under the influence of the ingestion of salts. Some other factor must be at work. Of what nature this is we cannot guess, but no clear conception is gained by using the term " washing out " of one salt by another without the intervention of diuresis.

Moreover, in Kozerski's experiments, the increase in chlorine excretion reached the amount necessary to neutralize the excess of sodium and potassium excreted, whence it follows that the salts themselves were excreted as carbonates; the other fixed acids in the urine were not increased. As an example of this the following figures taken from Kozerski's work are cited:

Number of Experiment.	*Total Chlorine Excretion.*	*Chlorine Equivalent of K_2O.*	*Chlorine Residue.*	*Excretion of Na_2O.*		*Difference, i.e., between Na_2O Excreted and Calculated from Chlorine.*	*Additional Na_2O.*	*Difference.*
				Calculated from Cl Residue.	Found.			
	Gm.	Gm.	Gm.	Gm.	Gm.	Gm.	Gm.	
1	13·14	1·95	11·19	9·70	9·51	0·26	—	−0·26
2	17·46	2·27	15·19	13·27	16·65	3·38	3·4	+0·02
3	14·95	2·47	11·48	10·90	18·44	8·44	9·4	+0·96
4	12·82	1·56	11·26	9·83	0·87	0·87	—	−0·87
								0·15

In this connection, moreover, it is of interest to note that increased alkali excretion can be brought about by very different circumstances. In some early and careful experiments on rabbits, Katsuyama produced alkali excretion with a variety of diuretic agents, and, what is of greater importance, to the same extent whether diuresis occurred or not (76).

8. Inorganic Acids.

The changes in acid excretion under the influence of alkalis elucidates the question as to whether alkalis act contrarily to acids in the sense of causing their excretion from the organism.

(*a*) *Hydrochloric Acid.*

In cases where there is no special chlorine hunger, as in Bunge's experiment already cited, the excretion of hydrochloric acid is increased correspondingly to that of the fixed alkalis.

(*b*) *Sulphuric Acid.*

Sulphuric acid excretion has been studied in men and dogs. Experiments on the former showed clearly that no change was brought about by the action of alkalis; in the latter, as we have already seen, there was a considerable diminution of the unoxidized sulphur.

(*c*) *Phosphoric Acid.*

The excretion of phosphorus is variously influenced by different kinds of alkalis. In the first place, there is a difference in the action of the true alkalis and the alkaline earths. The latter invariably decrease the excretion because they hinder the absorption of a portion of the phosphorus taken as food by the formation of insoluble phosphates in the intestine (71 to 75). Whether they also cause an excretion of phosphoric acid from the intestinal wall is uncertain; experiments on dogs show that phosphates injected subcutaneously are quantitatively excreted in the urine whether the intestine is deluged with calcium carbonate or not. We have already discussed the practical therapeutic application of this fact. In the case of the true alkalis the action appears to differ according as potassium and sodium are employed. Bunge and others have found the amount of phosphorus excreted uninfluenced by sodium salts. On the other hand, treatment by potassium salts caused a considerable fall in phosphorus excretion in nearly all Bunge's experiments. Without further observations the cause for this cannot be decided, but the following considerations appear of importance. On a normal diet herbivora excrete nearly all their phosphorus and calcium by the bowel. The urine is almost free from calcium and phosphorus, and remains so when the latter is given subcutaneously, this also passing out by the bowel. It is only on animal diet or during starvation that as much phosphoric acid and calcium are excreted in the urine of herbivora as of carnivora, whilst the latter also, on a vegetable diet, excrete these bodies in the fæces like herbivora. Thus the variation in the method of excretion is not due to the constitution of the animal, but to the nature of the diet. The cause does not lie in the alkalinity of a vegetable diet, as when the urine of carnivora in the above experiments was rendered alkaline by the administration of sodium the intestinal excretion of phosphorus was not increased. The exhibition of potassium, on the other hand, in the presence of a sufficiency of calcium in the diet led to an excretion of phosphoric acid in the fæces of carnivora, and we must thus seek for the explanation of the presence of phosphoric acid in the fæces in the relative richness in potassium and calcium in a

vegetable diet, and conversely with a diet of flesh. How, then, does the potassium act ? Bertram has cleared up the question by the observation that the exhibition of calcium citrate considerably decreases not only the phosphoric acid, but also the calcium in the urine (in one case within three days from 0·5 to 0·28 gramme), an action which is not shared by sodium.[1]

The cause of the varied action of potassium and sodium on calcium excretion in the urine is, according to Bertram, that the calcium phosphates found in the body fluids are insoluble in potassium carbonate, and hence cannot be excreted in the urine ; they are, however, soluble in the corresponding sodium compound.

LITERATURE.

1. Raimondi : Ueber die Alkalinität des Blutes und ihre künstl. Veränderungen in phys. und therap. Hinsicht betrachtet. An. u. **299.** 3. 1884 ; Ma. **1884.**

2. Salaskin u. Kowalewsky : Ueber den Ammoniak- und Milchsäuregeh. im Blute. Z. p. C. **35.** 552. 1902.

3. Freudberg : Ueber den Einfl. von Säuren und Alkalien auf die Alkaleszenz des Blutes. Ar. p. A. **125.** 566. 1891.

4. Loewy : Ueber den Einfl. der salin. Abführmittel auf den menschl. Gaswechsel. Ar. P. M. **43.** 515. 1888.

5. Livierato : Ueber die Schwankungen der vom Diabetiker ausgeschiedenen Kohlensäure. E. A. **25.** 161. 1889.

6. Lehmann : Ueber die Wirk. der Alkalien auf den respirat. Stoffwechsel. Tagebl. d. Naturf. Vers. Magdeburg. **1884.**

7. Chvostek : Der oxydative Stoffw. bei Säureintoxikation. C. i. M. **14.** 329. 1893.

8. Loewy : Bemerk. zur Wirk. der Borpräparate aus den Stoffwechsel. D. A. **1903.** 378.

9. Stadelmann : Ueber den Einfl. der Alkalien auf den menschl. Stoffwechsel. 1890.

10. Rost : Ueber die Wirk. der Borsäure und des Borax auf den tierischen und menschl. Körper. A. k. G. **19.** 1. 1902.

11. Rubner : Ueber die Wirkung der Borsäure auf den Stoffwechsel des Menschen. A. k. G. **19.** 70. 1902.

12. Seegen : Ueber die Aussch. des Stickstoffes der im Körper zersetzten Albuminate. S. W. A. **55.** 2. 1867.

13. Höfler : Ueber den Einfl. des Krankenheiler Quellsalzes auf den Stoffwechsel. D. m. W. **1888.** Nr. 23.

14. Rabuteau et Constant : Des actions des alcalins sur l'organisme. Gz. h. **2.** 7. 1870.

15. Kratschmer : Ueber Zucker und Harnstoffaussch. beim Diab. mell. unter dem Einfl. von Morphium, kohlensaurem und schwefelsaurem Natron. S. W. A. **66.** 1. 1872.

16. Damourette et Hyades : Einige Wirk. der Alkalien auf den Stoffwechsel. Bu. g. t. **7.** 441. 1881.

17. Münch : Cit. by Burchard (21).

18. Severin : Ueber die Einwirk. des Natriumkarbonats. Diss. Marburg, 1868.

19. Jawein : Über den Einfl. des Natriumkarbonats resp. -Zitrats in grossen Dosen gegeben auf den N-Umsatz. Z. M. **22.** 43. 1893.

20. Spilker : Ueber den Einfl. der Alkalien auf den Stoffwechsel. Diss. Berlin, 1889.

21. Burchard : Ueber den Einfl. des kohlensauren resp. zitronensauren Natrons auf den Stoffw. speziell auf die Stickstoffausscheid. By Stadelmann (9). P. 3.

22. Klemptner : Ueber die Stickstoff- und Harnsäureaussch. bei Zufuhr von kohlensaurem resp. zitronensaurem Natron. By Stadelmann (9). P. 37.

[1] The excretion of magnesium is not affected by either potassium or sodium.

23. Kozerski: Über den Einfluss des kohlensauren Natrons auf den menschl. Stoffwechsel. By Stadelmann (9). P. 142.
24. Strauss: Ueber die Einwirk. des kohlensauren Kalkes auf den menschl. Stoffwechsel. Z. M. **31.** 492. 1896.
25. Mayer: Ueber den Einfl. der Natriumsalze auf den Eiweissumsatz im Tierkörper. Z. M. **3.** 82. 1881.
26. Ott: Ueber den Einfl. des Natriumkarbonats und Kalziumkarbonats auf den Eiweissumsatz im Tierkörper. Z. B. **17.** 165. 1881.
27. Munk: Ueber das Verhalt. des Salmiaks im Organismus. Z. p. C. **2.** 29. 1878.
28. Rosemann: Ueber die Retention von Harnbestandteilen im Körper. Ar. P. M. **72.** 467. 1898.
29. Kaufmann: Ueber die Einwirk. von Medikamenten auf die Glykosurie des Diabetikers. Z. M. **48.** 260, 436. 1903.
30. Du Fourt: Einfl. der Alkalien auf die Glykogenbild. in der Leber. Ar. m. ex. **1890.** 424.
31. Külz: Beitr. zur Kenntnis des Glykogens. Festschr. für C. Ludwig. Marburg, 1890. P. 69.
32. Nebelthau: Zur Glykogenbild. in der Leber. Z. B. **28.** 138. 1891.
33. Richter: Zur Kennt. der Wirkungsweise gewisser die Zuckeraussch. herabsetzender Mittel. Z. M. **36.** 152. 1898.
34. Gans: Ueber den Einfl. von Salzlösungen auf die Umbild. des Glykogens in Zucker. K. i. M. **1896.** P. 449.
35. Ken Taniguti: Ueber den Einfl. der Alkalien auf die Oxydation im Organismus. Ar. p. A. **117.** 581. 1889.
36. Zerner: Ueber die chem. Bedingungen für die Bildung von Harnsäuresedimenten. W. k. W. **1893.** Nr. 15.
37. Ritter: Ueber die Bedingungen für die Entstehung harnsaurer Sedimente. Mü. m. W. **1895.** Nr. 8.
38. Smale: Beitr. zur Kenntnis der Lösungsbedingungen der Harnsäure im Harn. C. P. **9.** Nr. 12. 1895.
39. Herxheimer: Über die therap. Verwendung des Kalkbrotes. B. k. W. **1897.** Nr. 20.
40. von Noorden: Zur Behandl. der harnsauren Nierenkonkremente. K. i. M. **1896.** 308.
41. Schreiber u. Waldvogel: Beitr. zur Kenntnis der Harnsäureaussch. unter phys. und pathol. Verhältnissen. E. A. **42.** 69. 1899.
42. His: Die Aussch. von Harnsäure im Urin der Gichtkranken. D. Ar. M. **65.** 156. 1900.
43. Heffter: Die Aussch. des Schwefels im Harn. Ar. P. M. **38.** 476. 1886.
44. Laquer: Ueber die Ausscheidungsverhält. der Alloxurkörper im Harn von Gesunden und Kranken. K. i. M. **1896.** 333.
45. von Noorden: Ausnutzung der Nahrung bei Magenkranken. Z. M. **17.** 137, 452, 514. 1890.
46. Gorsky: Ueber den Einfl. des Lithiumkarbonats auf den Stoffw. des Gesunden. C. m. W. **1890.** 27.
47. Hagentorn: Ueber den Einfl. des kohlensauren und zitronensauren Natrons auf die Aussch. der Säuren im Harn. By Stadelmann (9). 91.
48. Kast: Ueber die antisept. Leistungen des Magensaftes. Festschr. z. Eröffn. d. neuen Hamburger Krankenhauses. 1889.
49. Ludwig: Ueber den Einfl. des Karlsbader Wassers auf den Stoffwechsel. C. i. M. **1896.** 1153, 1176.
50. Herrmann: Ueber die Abhängigkeit der Harnsäureaussch. von Nahrungsund Genussmitteln mit Rücksicht auf die Gicht. D. Ar. M. **43.** 273. 1888.
51. Chittenden and Cummins: Infl. of Some Organic and Inorgan. Substances on Gas Metabolism. Tr. Connect. Acad. 1886. VII.; Abstr. in Ma. **17.** 342. 1887.
52. Leber: Zur Physiol. und Pathol. der Harnsäureaussch. beim Menschen. B. k. W. **1897.** 44.
53. Walter: Ueber die Wirk. der Säuren auf den tier. Organismus. E. A. **7.** 148. 1877.
54. Coranda: Ueber das Verhalten des Ammoniaks im menschl. Organismus. E. A. **12.** 76. 1880.

55. Hallervorden: Ueber das Verhalt. des Ammon. im Organis. und seine Beziehung zur Harnstoffbildung. E. A. **10.** 125. 1878.

56. Auerbach: Zur Kenntnis der Aussch. des Phenols aus dem Tierkörper. Ar. p. A. **77.** 226. 1879.

57. Münzer: Der Stoffwechsel des Menschen bei akuter P-Vergiftung. D. Ar. M. **52.** 199. 1894.

58. Minkowski: Die Gicht. 1903.

59. Rosenfeld: Grundzüge der Behandl. der harnsauren Diathese. K. i. M. **18.** 96. 319.

60. Pfeiffer: Die Gicht und ihre erfolgreiche Behandlung. 1891.

61. L. Vogel: In von Noorden's Beitr. zur Lehre vom Stoffwechsel. 1894. Heft 2.

62. Levison: The Uric Acid Diathesis. Trans. by Scott. Lond. Cassell, 1894.

63. Biesenthal u. Schmidt: Piperazin bie Gicht und Steinleiden. B. k. W. **1891.** 1224.

64. Klemperer u. Zeissig, quoted by Klemperer: Über Gicht und harnsaure Nierensteine. 1896.

65. Magnus-Levy: Die Oxybuttersäure und ihre Beziehungen zum Coma diabeticum. 1899. **42.** 149.

66. Bunge: Ueber die Bedeutung des Kochsalzes und das Verhalten der Kalisalze im menschl. Organismus. Z. B. **9.** 104. 1873.

67. Gäthgens: Ueber Ammoniakaussch. Z. p. C. **4.** 36. 1880.

68. Kurtz: Ueber die Entziehung von Alkalien aus dem Tierkörper. Diss. Dorpat, 1874.

69. Reinson: Über die Aussch. des Kali und Natron. Diss. Dorpat, 1864.

70. Katsuyama: Ueber den Einfl. des Thein auf die Aussch. von Alkalien im Harn. Z. p. C. **28.** 587. 1899.—Katsuyama: Ueber den Einfl. einiger harntreibender Mittel auf die Aussch. von Alkalien im Harn. Ibid. **32.** 235. 1901.

71. Riesell: Ueber die P_2O_5-Aussch. im Harn bei Einnahme von kohlensaurem Kalk. M.-C. U. **3.** 319. 1868.

72. Lehmann: Zur Wirk. des kohlensauren Kalkes und der kohlensauren Magnesia. B. k. W. **1882.** 320.

73. Bertram: Aussch. der Phosphorsäure bei den Pflanzenfressern. Z. B. **14.** 335. 1878.

74. Tereg u. Arnold: Das Verhalten der Kalziumphosphate im Organis. des Fleischfressers. Ar. P. M. **32.** 122. 1883.

75. Bergmann: Ueber die Ausscheidungswege der Phosphorsäure beim Fleisch- und Pflanzenfresser. E. A. **47.** 77. 1902.

76. Wasbutzki: Ueber den Einfl. von Magengärungen auf die Fäulnisvorgänge im Darmkanal. E. A. **26.** 133. 1889.

77. C. E. Simon: The Modern Aspect of Indicanuria. A. J. M. S. 1895. **110.** Pp. 48, 157.

78. Biernatzki: Ueber die Darmfäulnis bei Nierenentzündung und bei Ikterus. Ar. M. **49.** 87. 1891.

79. Schmitz: Zur Kenntnis der Darmfäulnis. Z. p. C. **17.** 401. 1892.

80. Gerhardt: Zur Lehre von der Achylia gastrica. B. k. W. **1898.** 765.

81. Strauss: Resorp. und Stoffwech. bei Achylia gastrica. Z. M. **41.** 280. 1900.

82. Hofmann: Stoffwechselunters. nach totaler Magenresektion. Mü. m. W. **1898.** 560.

83. Schlatter: Case of Total Extirpation of the Stomach. Lancet. **2.** 1898. P. 1314.

84. Gerhardt: Ueber Darmfäulnis. Er. Ph. III. **1.** 107. 1904.

85. von Tabora: Grenzwerte der Eiweissausnutz. bei Störungen der Magensaftsekretion. Z. M. **53.** 461. 1904.—von Tabora: Ueber die Beziehungen zwischen Magensaftsek. und Darmfäulnis. D. Ar. M. **87.** 254. 1906.

86. Fawcett: On Piperazin. Gu. H. Rep. **51.** 67. 1894.

IV.—BORIC ACID AND BORAX.

The action of this group, as far as it is known, closely resembles that of the alkalis. Boric acid and borax may correctly be described together, owing to the very slight acid properties of the former ; this is shown by the fact that even large doses do not increase the NH_3 excretion.

The boron preparations have been the subject of much recent investigation owing to their extensive use as food preservatives. Owing to the statement that boron preparations give rise to a marked loss of weight in man (2), their influence on gaseous metabolism has been studied by the large calorimeter (1). The loss of weight, as has previously been shown, is by no means invariable (3). During the first seven days of a " borax period," Neumann, in a very exact experiment on himself, lost 1,200 grammes in weight (nearly 3 pounds) ; during the next three days he put on 500 grammes (over 1 pound) ; while during the second " borax period " his weight underwent no change (4). Experiments on dogs showed no regular loss of weight (5, 2). Rubner, in his two series of experiments on man, had shown a rise in fat metabolism on daily doses of 3 grammes of borax ; these increases, however, were not so great as the loss of weight in other cases might lead one to expect (6). Moreover, the rise varied considerably in the two series of experiments : in one case it was 29 per cent., and in the other 10 per cent. Corresponding experiments have been made by Loewy on two dogs, one normal and one castrated. The gaseous exchange during rest was estimated by the Geppert-Zuntz method in the latter, 3 grammes of borax being administered daily over a period of eleven days. There was a rise of 40 per cent. in the gaseous metabolism. In the first animal no change was observed, although it was under the influence of borax for six days longer than the castrated animal. A consideration of these experiments suggests that the action of the borax depends upon individual proclivities.

That it is not specific for borax, but depends more on simple alkali, or rather salt effect, is seen on comparison with the experiment detailed above (p. 1071), in which a splayed bitch, after a dose of 3 grammes of soda for twelve consecutive days, showed an increase of gaseous metabolism equal to that after borax (30 per cent.).

As in the case of the alkalis, the action of borax on protein metabolism has been the subject of very numerous investigations, probably for the same reason—viz., the failure to obtain uniform results. In man a daily intake of 3 grammes of boric acid impairs absorption and slightly decreases the output of urea (7). The impairment of absorption may be noted after as little as 0·5 gramme of boric acid has been added to the food. This observation has been several times confirmed (8). By varying the plan of the experiment, it has been shown that this decreased absorption is apparently the result of an increased peristalsis—often amounting to diarrhœa—which takes place a few hours after food is ingested. Tunnicliffe and others (4, 9) have found that moderate

doses do not increase protein metabolism ; in fact, in one case there was a slight fall in urea excretion. Rost's careful experiments on different individuals showed sometimes an increase and sometimes no change in the nitrogenous excretion. As was often observed in the case of the alkalis, the figures rose and fell abruptly on certain days.

As to animal experiments, M. Gruber (10) found that large doses acted like alkalis in raising protein metabolism, possibly on account of increased loss of water. Chittenden and Giess found that moderate doses, insufficient to produce the effect of salts, failed to disturb nitrogenous equilibrium. Rost's experiments gave no constant results. Apart from impeding absorption, boric acid and borax do not appear to exert any specific influence on protein metabolism, but act exactly like the neutral salts, causing an increase owing to their diuretic action. In some cases they may, however, lead to a slight decrease ; in others they do not produce any change.

LITERATURE.

1. Rubner : Ueber die Wirk. der Borsäure auf den Stoffw. des Menschen. A. k. G. **19.** 70. 1902.
2. Rost : Ueber die Wirk. der Borsäure und des Borax auf den tierischen und menschlichen Körper. Ibid. **19.** 1. 1902.
3. Weber : Ueber die Beeinflussung des Stoffw. durch einige pharm. wichtige Stoffe. Er. Ph. III. **1.** 233. 1904.
4. Neumann : Ueber den Einfl. des Borax auf den Stoffw. des Menschen. A. k. G. **19.** 89. 1902.
5. Chittenden and Giess : The Influence of Borax and Boric Acid upon Nutrition, with Special Ref. to Proteid Metab. A. J. P. **1.** 1. 1898.
6. Loewy : Bemerk. zur Wirk. der Borpräparate auf den Stoffwechsel. V. p. G. **1902.** 45.
7. Forster : Ueber die Verwendbarkeit der Borsäure zur Konservierung von Nahrungsmitteln. Ar. Hy. **2.** 75. 1884.
8. Heffter : Ueber den Einfl. der Borsäure auf die Ausnutzung der Nahrung. A. k. G. **19.** 1902.
9. Tunnicliffe and Rosenheim : On the Influence of Boric Acid and Borax upon the General Metab. of Children. J. Hy. **1.** 168. 1901.
10. Gruber : Ueber den Einfl. des Borax auf die Eiweisszersetz. im Organismus. Z. B. **16.** 198. 1880.

V.—POISONS WHICH PRODUCE SYMPTOMS CHARACTERISTIC OF WANT OF OXYGEN.

The life processes of animals[1] normally depend chiefly upon the oxidation of foodstuffs. If the supply of oxygen is limited, certain changes occur which vary according to the degree of deprivation of oxygen ; if this is relatively slight, but continuous—as, for instance, during residence at high altitudes—a new formation of erythrocytes and hæmoglobin occurs (1 to 3) ; there is usually at the same time an increased gaseous exchange (4), and there is protein increase. All these

[1] Anaerobic bacteria are no real exception. In the first place, they are generally classed among plants, not animals ; and, in the second place, they only differ from other plants in not obtaining oxygen from the air.

phenomena are probably the result of over-compensation (5) ; on a return to lower levels they are reversed, but if anæmia had formerly existed, the increased action of the blood-forming organs produced by life at high altitudes continues (6). Excessive deprivation of oxygen acts in a very different manner, as will be seen by certain circumstances to be mentioned later—the experiments being mostly of short duration. In these, by help of the oxygen stored in the organism, the vital processes could at first be maintained for some time to a normal degree, but not in the normal manner. This explains to a great extent the process occurring in anaerobes ; it is in reality probably a decomposition process. A partial or local anaerobiosis also occurs normally, as when, for example, the special demands of one particular organ set up temporarily a relative want of O_2 elsewhere.

The poisons which interfere with the absorption of oxygen can produce this condition in various ways :

1. *Those which prevent the proper oxygenation of the tissues* (*a*) by chemical changes in the erythrocytes and their function—to this class belong carbon monoxide on the one hand, and certain other bodies on the other, each of which will be separately dealt with ; (*b*) by influencing such processes as respiration and circulation, which maintain the normal oxygenation of the blood—to this class belong, among others, the narcotics, curare in the absence of artificial respiration, etc. ; (*c*) by increasing oxygen consumption whilst the supply remains normal, thus causing a relative want of oxygen—in this class come the tetanizing poisons—*e.g.*, strychnine.

2. *Those which decrease the oxidative power of the tissues by a direct influence on them.* In this class, in the first place, comes prussic acid ; to a certain extent, as will later on be shown in detail, a similar action occurs with phosphorus, arsenic, and certain of the heavy metals, such as iron, mercury, and antimony.[1] At any rate, in poisoning with all these substances, many of the chemical symptoms resemble those produced by deficiency of oxygen, though there is no evidence that the amount or nature of the oxygen supply to the cells is in any way altered. The possibility is strengthened by the fact that small doses of these substances, as far as has been ascertained, cause a similar group of symptoms as are produced by a slight limitation in oxygen supply (residence at high altitudes), and that toxic doses produce a condition resembling asphyxia.

LITERATURE.

1. Miescher : Ueber die Beziehungen zwischen Meereshöhe und Beschaffenheit des Blutes. (*a*) K. S. 1893. 809 ; (*b*) Histochem. und physiol. Arbeiten. 1897. II. 328.

2. Cohnheim : Physiol. des Alpinismus. Er. Ph. 2. 1. 612. 1903.

[1] The organic substances which belong to this class include oleum pulegii (oil of pennyroyal), which acts very similarly to phosphorus ; the halogen narcotics, like chloroform, when administered internally or subcutaneously ; and chloral hydrate, whose action resembles that of the narcotics. Whether the antiseptics, such as phenol, salicylic acid, and their derivatives, should be included cannot be decided at present. The little we know of the metabolism under cantharides makes it advisable to include it in an account of the metals.

3. Zuntz, Loewy, Müller, Caspary: Höhenklima und Bergwanderungen in ihrer Wirk. auf den Menschen. 1906. 172 ff.
4. Jaquet u. Stähelin: Stoffwechselv. im Hochgebirge. E. A. 46. 274. 1901.
5. Miescher: l. c. 1 (*b*), p. 351.
6. Ibid., p. 337.

A.—BLOOD POISONS.

1. Carbon Monoxide.

The essential peculiarity of poisoning by carbon monoxide is the power of the gas to form a stable compound with hæmoglobin, so that the latter cannot fully exercise its function as an oxygen carrier. Very exact investigations by Haldane and others have shown how the presence of oxygen and carbon monoxide in varying proportions affect the combinations of the hæmoglobin (1 to 5). The question as to whether CO has any specific toxic action, or whether its effects are due to the exclusion of oxygen, has been much disputed. The majority of authors (6 to 12) incline to the latter theory, on the ground that it is observed that a supply of oxygen rapidly relieves the disturbance (8, 22 to 24), and because of the fact that animals which possess no hæmoglobin, like insects, stand CO without harm. Other investigators (13 to 15) hold the opinion that the action is not due to absence of oxygen on the ground that certain other after-symptoms appear in cases of poisoning in man (15 to 21). It is difficult to decide which view is correct, especially as it is not possible experimentally to produce a deficiency of oxygen such as occurs when increasing quantities of CO are slowly mixed with the inspired air (20) in any other way.

(*a*) *The Blood Gases.*

The blood gases in carbon monoxide poisoning have been investigated in animals by Saike and Wakayama (2, 25), whose results are tabulated below:

Normal Rabbit.		*Normal Dog.*	
CO_2 Volume.	O_2 per Cent.	CO_2 Volume.	O_2 per Cent.
30·00	12·64	30–40	20·00
CO-Poisoning.		CO-Poisoning.	
9·26	4·74	16·75	6·26
8·63	5·62	16·59	6·20
7·23	5·55	3·22	2·01
5·21	7·62	—	—

It is easy to see how it is that the amount of oxygen which may be withdrawn decreases, considering the method of action of CO as already explained; it is also easy to see why the amount of the decrease varies under different conditions of intoxication. On the other hand, the behaviour of the carbon dioxide requires special explanation. As is seen by the table, the amount of the gas also decreases regularly and at times excessively. Various possible causes have been assigned for this.

1. Decreased formation owing to an intoxication of the tissues, which retards oxidation. This cannot be regarded as the only, or only important, causative factor, because Meyer (27), some years ago, showed that a very large diminution of CO_2 formation only causes a quite gradual and trivial fall in the proportion found in the blood.

2. Improved aeration of the blood owing to increased respiration. Carbon monoxide poisoning, however, does not so influence the respiration that any increased passage of CO_2 from the blood into the expired air can be ensured. The fact that the blood for gas analysis was first taken a much longer time after the poisoning than Ewald showed was necessary for the restoration of the normal proportion of CO_2 is against this factor taking any important share in the phenomenon (28).

3. Decrease in the alkalinity of the blood. In the majority of cases of decrease of CO_2 in the blood this is the principal cause. Various considerations show that at any rate the most important fact in CO-poisoning is an increase in the acidity of the blood. In the first place, a diminution in alkalinity has been determined by titration (29); then it has been shown in fowls that during CO-poisoning the amount of sarcolactic acid in the blood rises from about 0·0269 per cent. to 0·1227 per cent.[1]

The fact that in dogs, who generally react to acid-poisoning by only a slight decrease in the amount of CO_2 in the blood (31), the latter sinks so low is no objection to the view that the cause is an acidosis. Results may occur when acids are given by the mouth differing from those which appear when they are formed in the tissues, as in the latter case they probably combine with the fixed alkalis on the spot before they can be neutralized by ammonia. In dogs, moreover, the direct introduction causes a marked fall in the carbon dioxide.

The next question is as to the cause of the acidity of the blood. It must first be shown that deprivation of oxygen influences the alkalinity of the blood.

Galeotti (33) found in himself and others a reduction of the alkalinity of the blood of about 40 per cent. after some days' stay on Monte Rosa. He also showed a much slighter diminution in animals which for some hours had inspired an atmosphere poor in oxygen. A decrease in the CO_2 content of the blood was also found in animals by Mosso and Marro (34).

[1] It is not, of course, implied that other acids do not circulate in increased amounts in the blood. Apparently—at least, in the case of sulphuric and phosphoric acids—this is the result of protein metabolism, as the latter is increased.

It can, then, be regarded as certain that the decrease in alkalinity in the blood in CO-poisoning is due to deprivation of oxygen, for this produces an acidosis of the organism dependent for its degree on the oxygen requirements of the cells.[1]

(b) Gaseous Metabolism.

It is very difficult to decide experimentally the question as to whether oxidation processes are specifically affected by CO, or whether they merely suffer from a diminution of the oxygen supply. It is hardly possible to arrange absolutely comparable quantitative experiments showing the results of scarcity of oxygen produced by carbon monoxide and that produced in other ways. So we must content ourselves with evidence that certain similarities exist between the gaseous metabolism in CO-poisoning and in conditions of poverty of oxygen, such as that produced by rarefaction of the atmosphere. In contrast to the great number of experiments on the results of diminished supply of oxygen on metabolism (35 to 37, 45), the number of observations on metabolism in CO-poisoning is very small. By means of a special technique it was shown that a dog breathing air containing 0·2 per cent. CO—so that less than half the Hb was saturated with O_2—inspired the normal amount of oxygen, but expired considerably more than the normal amount of CO_2 (39). The same result has been obtained in various degrees when the supply of oxygen was decreased by other methods. The fact that with a certain extent of poisoning the intake of O_2 remains unchanged can only be explained by supposing that the much diminished functional activity of the Hb is compensated by deeper breathing, which usually occurs both in CO-poisoning and in other conditions of diminished O_2 supply. Naturally, this compensation is only possible in any case up to a certain point, so that in deep intoxication the O_2 intake is observed to fall (40). Moreover, an unaltered O_2 intake, in spite of increased respiratory movements, means a relative fall in O_2 intake, which becomes absolute, as we have seen, in more extreme cases. The cause of the latter is doubtless a disturbance in the oxidizing activity of the tissues owing to extreme want of oxygen. The fact that the output of CO_2 is increased can be explained on various grounds. That it does not decrease is in consonance with what is observed very often in conditions of marked scarcity of oxygen—namely, that for some time the CO_2 output continues unaltered, probably owing to some different form of metabolism to that which occurs with a normal O_2 supply. Under these conditions the CO_2 output is probably not less than normal, having regard to the increased respiratory activity. But the increase in excretion must not be referred entirely to a merely probable increase in production. It is more likely that the increased ventilation of the blood is due to increased respiratory action consequent on the expulsion of CO_2 from its chemical combination in the blood by stronger acids (*vide supra*).

[1] Probably the comatose condition of those poisoned by coal gas is sometimes mainly caused by this acidosis, and may be favourably influenced by the exhibition of soda, though specific damage to the cerebral centres from prolonged deprivation of oxygen cannot be excluded as a cause.

We must, then, conclude that gaseous metabolism in carbon monoxide poisoning does not differ from that in simple deprivation of oxygen; with certain degrees of poisoning the interchange resembles the normal, but is raised by increased muscular activity. In the deeper intoxications it is diminished. The chemical interchange is invariably abnormal—namely, anaerobiotic.

(*c*) *Protein Metabolism.*

In man the excretion of nitrogen is considerably increased immediately on the cessation of poisoning and for two or three days afterwards (42, 43); the same thing has been observed in dogs (44, 45), the increase being much greater in starving animals (50 per cent. as compared with 15 per cent.). The following table contains Jeanneret's results (44):

Day.	*Amount from 7 p.m. to 7 a.m.*		*Amount from 7 a.m. to 12.30 Noon.*		*Amount from 12.30 Noon to 7 p.m.*		*Twenty-four Hours.*	
	Urine.	Urea.	Urine.	Urea.	Urine.	Urea.	Urine.	Urea.
	c.c.	Gm.	c.c.	Gm.	c.c.	Gm.	c.c.	Gm.
1	110	7·3	130	3·2	90	2·7	320	13·2
2	126	8·1	186	3·2	95	2·5	407	13·8
3	105	8·0	153	3·1	65	2·9	323	13·9
4	115	8·2	130	3·0	75	2·5	319	13·8
5[1]	116	9·0	140	2·8	220	4·6	476	16·4

The cause of this increase in protein metabolism is undoubtedly the diminution in oxygen supply, and the question then arises as to how this is brought about. The theory that it is due to increased diuresis (46) has been disproved by the fact that the increase in nitrogen is often first noted when the diuresis has ceased (47, 48). Again, the great difference observed in fasting and feeding animals is against this theory. It must be a condition of increased protein decomposition, which, indeed, is often compensated by a subsequent retention. This increased decomposition may be primarily due to a direct injury to the protoplasm owing to deficiency in oxygen, or, secondarily, owing to some interference with the use of non-nitrogenous material.

The latter supposition may be excluded, as in this case there would have to be increased urea excretion *during* the intoxication, since Speck has recently proved most conclusively that urea formed by the oxidation of protoplasm is excreted with marked rapidity. But even if we suppose that during the intoxication only the non-nitrogenous moiety of the protoplasm is oxidized, we have no right to suppose that the organism has not the power to burn up the fats and carbohydrates. Relying, therefore, on the classical statements of Fraenkel and Miescher (49), we must regard the increased excretion of nitrogen as the expression of a primary damage

[1] Poisoning with CO from 7 a.m. to 12.30 noon.

to the cell protoplasm, which is broken up owing to the deficiency of oxygen, at first into fragments incapable of excretion. The oxidation into urea occurs subsequently, owing to the need of the organism for fuel and a supply of oxygen.

The experiments of Miescher and others (50 to 52), and Jacoby's recent researches into auto-digestion of organs (53), render it probable that an excessive fermentative protein decomposition takes place in the absence of an adequate supply of O_2. To account for the increase in nitrogen excretion observed in fasting animals, it has been supposed that the increased activity of the respiratory muscles is partly provided for by protein, which, as usual, gives rise to work and heat; this must be added to the amount decomposed owing to want of oxygen. It seems, however, more likely that, owing to the presence of non-nitrogenous material in the feeding animal, a partial resynthesis occurs between these and the products of protein decomposition.

(*d*) *The Distribution of the Urinary Nitrogen.*

In a severe case of carbon monoxide poisoning in man there was only a very slight increase in the urinary ammonia, but there was the remarkably high uric acid excretion of 3 grammes. On the next day there was a return to the normal (43). This was not observed in other cases, but has been confirmed by Noel Paton (55). The ammonia excretion has also been observed in animals (54). Amino-acids have not been found in experimental cases, but it seems probable that they are present in small amounts in the urine in CO-poisoning (56).

(*e*) *Excretion of the Inorganic Constituents of Urine.*

The excretion of phosphorus closely corresponds to that of nitrogen. This has also been observed in dyspnœa (57). There are no estimations of the total sulphur extant, but it is safe to assume that the sulphur is raised as in experiments with oxygen deficiency, and there is a rise in the amount of so-called "neutral" sulphur without any change in the sulphuric acid excretion (58).

With regard to the excretion of chlorine, dogs, if rich in chlorine, show a marked decrease in the urinary chlorides, an increase if they are not rich in chlorine (59). There is no clear explanation of this.

(*f*) *Abnormal Urinary Constituents.*

Lactic acid is found in CO-poisoning just as it is in cases of deficiency of O_2 due to anæmia (62) and dyspnœa (54, 60); it occurs in men, in fed and in starved dogs and rabbits (62), and has been identified as sarcolactic acid.

The increase in the blood has already been noted (61); less than the

normal amount has been found in muscle (63). These facts suggest the following questions :

1. Is the oxidation of lactic acid interfered with ?
2. Is the formation of lactic acid increased ?
3. Is more lactic acid formed and less oxidized ?

1. That the oxidation of lactic acid is diminished is shown by the fact that if injected subcutaneously it passes into the urine unchanged (64).

2. It cannot be determined with certainty whether more lactic acid is formed. The increased amount in the blood might be due merely to diminished oxidation. At any rate, the observed increase in lactic acid in muscle cannot be held to prove the contrary ; it merely makes it probable that no increased formation takes place in muscle. It may occur, however, in other organs ; in arsenical poisoning the amount found in different organs varies considerably (65). There are, however, no analyses of other organs in CO-poisoning. It is probable that more lactic acid is actually formed, and that it arises from carbohydrate, for in another example of relative oxygen privation (namely, overlying) the liver, when removed from the body, readily formed lactic acid. If this were so, it would explain the small amount of lactic acid found in muscle.

Observations of the most varied nature [Embden, Lusk, Mandel (65-67)] make it most probable that it is not only outside the body (*cf.* arsenic) that carbohydrates may yield lactic acid, which, however, does not imply that they are its only source (68). Though it cannot be absolutely denied that muscles have the power of forming glycogen, it is certain that the liver furnishes carbohydrate in accordance with the muscle requirements. In CO-poisoning the liver loses glycogen ; either it converts it into sugar which passes into the urine, or, under the influence of want of oxygen, it forms lactic acid, which is then excreted by the kidneys.[1] In both cases the muscle will obtain less glycogen than normal, and so less material for the manufacture of lactic acid. Hence, in CO-poisoning, the formation of lactic acid (probably from glucose) is increased, and also its oxidation is diminished.

Glucose is often present in the urine, but not always, even after severe CO-poisoning (69 to 80). The excretion begins during the intoxication, generally with marked diuresis, and appears to be checked by the establishment of the increased nitrogen excretion.

The proximate cause of the glycosuria is hyperglycæmia, which has been found in dogs and fowls (82). This, again, is caused by destruction of glycogen of the liver—at any rate, very little was found in the livers of CO-poisoned animals (83) ; on the other hand, glycosuria did not occur in fasting animals. The length of the fast necessary to prevent glycosuria varied considerably ; then, after an exactly similar previous diet, there was no sugar in one case on the third and in another on the ninth day. Moreover, it also failed to occur when the hepatic artery was tied, and when acid was injected into the liver (84). But the occurrence of glycosuria does not only depend on whether the intoxication is estab-

[1] Digestion experiments with the liver render it probable that it has this power. Similar experiments with muscle gave negative results.

lished when the animal is being fed or fasting, but also on the kind of food it has previously taken. This explains why glycosuria does not always occur.

A diet of flesh alone disposes dogs to glycosuria. Anomalous results with dogs in nitrogenous equilibrium, and others fed on flesh only, are explained, though doubtfully, as due to the slightness of the intoxication. In one instance, at any rate, this explanation will not hold good, as the dog, after a week on meat only, excreted no sugar in spite of a most severe intoxication. Some special factor must have co-operated in this case.

A diet with excess of carbohydrates (bread and sugar) appears not to favour the appearance of glycosuria according to Straub's experiments, whereas Rosenstein noted a maximum of sugar on a similar diet. As against Straub's experiments on dogs may be mentioned cases in man in which there was slight alimentary glycosuria. In rabbits fed on carbohydrates, Araki regularly found sugar; others have found it in starving and also in well-fed ducks, but in these and in geese the results are not uniform.

On the observation that glycosuria was favoured by a meat diet, Rosenstein and Vamossy tried to isolate the glycogenic moiety from the products of tryptic digestion of fibrin. They thought that the mono-amino acids rather than the diamino acids and peptones were the more active (86). Weber (86) actually produced a marked glycosuria in poisoned dogs which, before fasting, had been given only aspartic and glutamic acids (mono-amino diacids).

These researches, which were carried out without any control of the general metabolism, or, at least, without an effective control, are not sufficient to determine the opposing influences of carbohydrate or protein diet. We are not yet in a position to say whether the substances after the injection of which glycosuria appeared themselves afforded material for sugar formation, or only indirectly stimulated its production from pre-existing glycogen.[1]

Just as it is in CO-poisoning, so in all cases of deficient O_2-supply the occurrence of sugar in the urine is very variable, especially in man (87). In animals the results are more constant.

Albumin, as in all intoxications producing a deficient supply of oxygen, is almost invariably present in the urine.

In addition to this, the synthesis of hippuric acid and of the ethereal sulphates is decreased (88 to 90).

LITERATURE.

1. Bohr: See Loewy and Zuntz (8).
2. Bock: Die Dissoziationskurve des CO-Hämoglobins. C. P. **1894.** Nr. 12.
3. Hüfner: Ueber die Verteil. des Blutfarbst. zwischen CO und O_2. Z. p. C. **68.** 1884.
4. Haldane: The Relation of the Action of CO to Oxygen Tension. J. P. **18.** 201. 1896.

[1] As the destruction of glycogen was also noted in the animals fed on carbohydrate which had no tendency to glycosuria, experimental proof is wanted as to whether in these cases lactic acid is formed from glycogen.

5. Gréhant: Loi de l'absorption de l'oxyde de carbone par le sang d'un mammifère vivant. C. r. S. B. **46.** 344. 1895.
6. Fränkel: Ueber den Einfl. der veränderten Sauerstoffzufuhr zu den Geweben auf den Eiweisszerfall im Tierkörper. Ar. p. A. **67.** 273. 1876.
7. Hoppe-Seyler: Beitr. zur Kennt. des Stoffw. bei O_2-Mangel. Virch. Festschr. 1891.
8. Loewy u. Zuntz: Die physiol. Grundlagen der Sauerstofftther. In Michaelis' Handb. der Sauerstofftherapie. 1906. P. 34.
9. Haldane: l. c., p. 217.
10. Kunkel: Die Wirk. des CO auf kaltblütige Tiere. Beitr. z. Phys. Festschr. f. A. Fick. 1899. 53.
11. Mosso: La respiraz. nelle galerie et l'azione dell ossido di carbonio. 1900. 322.
12. Wachholz: Das Schicksal des CO im Tierkörper. Ar. P. M. **77.** 338. 1899.
13. Linossier: Beitr. zum Stud. der CO-Vergiftung. C. r. S. B. **41.** 1. 1890.
14. Geppert: CO-Vergift. und Erstickung. D. m. W. **1892.** Nr. 19.
15. Runeberg: Drei Fälle von CO-Vergiftung. C. k. m. **1903.** 791.
16. Becker: Ueber Nachkrankh. der CO-Vergiftung. D. m. W. **1889.** Nr. 26-28.
17. Rendu: Trophische Störungen infolge CO-Asphyxie. U. m. **1891.** Nr. 41.
18. Stolper: Die CO-Vergift. in gerichtlich-medizin. Hinsicht. Zt. f. Medizinal-Beamte. **1897.** Nr. 4.
19. Panski: Ein Fall von dissem. Myelitis nach CO-Vergiftung, etc. N. C. **1902.** Nr. 6.
20. Zuntz: Beitr. zur Kenntnis der Einwirk. der Atmung auf den Kreislauf. Ar. P. M. **17.** 374.
21. Sibelius: Zur Kennt. der Gehirnkrankh. nach CO-Vergiftung. Z. M. **49.** 111. 1903.
22. Kühne: Cit. by Loewy u. Zuntz (8).
23. Haldane: l. c. (4). Also, The Action of Carbon Oxide on Man. J. P. **18.** 430. 1896.
24. Gréhant: Traitem. par l'oxygène à la pression atmosph. de l'homme. C. r. A. S. **137.** 574.
25. Saiki u. Wakayama: Ueber die Wirk. des CO auf den CO_2-Gehalt des arteriellen Blutes. Z. p. C. **34.** 96. 1901.
26. Fränkel u. Geppert: Ueber die Wirk. der verdünnten Luft auf den Organismus. 1883.
27. Meyer: Über die Alkaleszenz des Blutes. E. A. **17.** 304. 1883.
28. Ewald: Zur Kenntnis der Apnoe. Ar. P. M. **7.** 575. 1883.
29. Araki: Ueber die chem. Aenderungen der Lebensprozesse infolge von O_2-Mangel. Z. p. C. **19.** 422. 1894.
30. Saito u. Katsuyama: Beitr. zur Kenntnis der Milchsäurebild. im tier. Organismus bei O_2-Mangel. Z. p. C. **32.** 214. 1901.
31. Walter: Ueber die Wirk. der Säuren auf den tier. Organismus. E. A. **7.** 148. 1877.
32. Spiro: Beitr. zur Lehre von der Säurevergift. beim Hund und Kaninchen. Be. P. P. **1.** 269. 1901.
33. Galeotti: Die Veränderungen der Alkalinität des Blutes auf der Kuppe des M. Rosa. Atti della r. acc. die Lincei. **12.** 646. 1903.
34. Mosso u. Marro: Die Veränderungen der Blutgase auf der Kuppe des M. Rosa. Ibid. **12.** 466. 1903.
35. Speck: Ueber Kraft- und Ernährungsstoffw. Er. Ph. **2.** 1. 1. 1903.
36. Jaquet: Der respirat. Gaswechsel. Er. Ph. **2.** 1. 457. 1903.
37. Loewy: Respirat. und Zirkulation bei Aenderung des Druckes und des O_2-Gehaltes der Luft. 1895.
38. Terray: Ueber den Einfl. des O_2-Gehaltes der Luft auf den Stoffw. Ar. P. M. **65.** 397. 1897.
39. Bock: Der respirat. Stoffwechsel während der CO-Vergiftung. Diss. 1895.
40. Desplats: Nouv. méthode directe pour l'étude de la chaleur animale. J. A. P. **22.** 213. 1886.

41. Wakayama: Cit. by Saito and Katsuyama (30).
42. Marthen: Beitr. zur Kenntnis der CO-Vergiftung. Ar. p. A. **136.** 535. 1894.
43. Münzer u. Palma: Ueber den Stoffw. des Menschen bei CO- und Nitrobenzolvergiftung. Z. H. **15.** 185. 1896.
44. Jeanneret: Der Harnstoff beim künstl. Diabetes. Diss. Bern, 1872.
45. Fränkel: Ueber den Einfl. der veränderten O_2-Zufuhr zu den Geweben auf den Eiweisszerfall im Tierkörper. Ar. p. A. **67.** 273. 1876.
46. Eichhorst: Ueber den Einfl. behinderten Lungengaswech. beim Menschen auf den N-Gehalt im Harn. Ar. p. A. **70.** 56, 74, 201. 1877.
47. Fränkel: Einige Bemerk. zu dem Aufsatz des Herrn Eichhorst. Ar. p. A. **71.** 117. 1877.
48. Pentzoldt u. Fleischer: Exper. Beitr. zur Pathol. des Stoffwechsels. Ibid. **87.** 241. 1879.
49. Miescher: Histochem. und physiol. Arbeiten. 1897, p. 116.
50. F. Miescher: l. c., p. 97.
51. Gautier et Landi: Fonctionnement anaérobie des tissus animaux. Ar. P. **1893.** 1.
52. Salkowski: Ueber ferment. Prozesse in den Geweben. D. A. **1890.** 354.
53. Jacoby: Ueber die Bedeut. der intrazellulären Fermente, etc. Er. Ph. **1.** 1. 213. 1902.
54. Araki: Ueber die Aenderung der chem. Lebensprozesse infolge von O_2-Mangel. Z. p. C. **19.** 422. 1893.
55. Noel Paton and Eason: On a Method of Estimating the Interference with the Hepatic Metabolism produced by Drugs. J. P. **26.** 166. 1901.
56. Loewy: Ueber Störungen des Eiweiss-stoffw. beim Höhenaufenthalt. D. m. W. **1905.** 48.
57. Reale u. Boeri: Ueber die im Gefolge von O_2-Mangel im Organismus auftretenden Stoffwechselstörungen. W. m. W. **1895.** P. 1063 *et seq.*
58. Benedikt: Der Einfluss pathol. Umstände auf die Aussch. des Schwefels. Z. M. **36.** 1898.
59. Kast: Ueber Beziehungen der Chloraussch. zum Gesamtstoffw. Z. p. C. **12.** 267. 1888.
60. Irisawa: Ueber Milchsäure im Blut und Harn. Z. p. C. **17.** 340. 1892.
61. Saito u. Katsuyama: l. c. (30).
62. Araki: l. c., p. 438.
63. Heffter: Beitr. zur Chemie des quergestreiften Muskels, etc. E. A. **31.** 225. 1893.
64. Araki: l. c., p. 455.
65. Morishima: Ueber das Vorkom. der Milchsäure im tier. Organismus mit Berücksichtigung der Arsenvergiftung. E. A. **43.** 217. 1899.
66. Embden: C. P. **18.** 832. 1905.
67. Lusk and Mandel: Lactic Acid in Intramediary Metabolism. A. J. P. **16.** 129. 1906.
68. Fürth: Ueber chem. Zustandsänderungen des Muskels. Er. Ph. II. **1.** 575. 1903.
69. Kahler: Erfahrungen über die Glykosurie bei CO-Vergiftungen. P. W. **1881.** Nrs. 48, 49.
70. von Jaksch: Ueber Glykosurie bei CO-Vergiftung. P. W. **1882.** Nr. 17. Z. M. **8.** 1884.
71. von Frerichs: Diabetes. **1884.** P. 25.
72. Richardson: M. T. **1.** 233. 1862.
73. Claude Bernard: Leçons sur les effets des substances toxiques et médicamenteuses. 1857. P. 161.
74. von Friedberg: Die Vergift. durch Kohlendunst. 1865.
75. Senff: Ueber den Diab. nach der CO-Atmung. Diss. Dorpat, 1869.
76. Thiel: Experiment. Glykosurie. Diss. Königsberg, 1887.
77. Weintraud: Ueber den Pankreadiab. der Vögel. E. A. **34.** 303. 1894.
78. Straub: Ueber die Beding. des Auftretens der Glykosurie nach der CO-Vergiftung. E. A. **38.** 139. 1897.
79. Rosenstein: Ueber den Einfl. der Nahrung auf die Zuckeraussch. beim CO-Diabetes. Diss. Berlin, 1897.

80. von Vamossy: Beitr. zur Kenntnis des CO-Diabetes. E. A. **41.** 273. 1898.
81. Heinsberg: Ueber die Einwirk der $CHCl_3$-Narkose auf den Kohlehydratbestand des tier. Organismus. Diss. Würzb., 1895.
82. Saiki u. Wakayama: Ueber die Wirk. des CO auf den Kohlensäuregeh. des Blutes. Z. p. C. **34.** 96. 1901.
83. Ottow: Ueber den Glykogengeh. der Leber nach CO-Vergiftung. Diss. Würzb., 1893.
84. Pick: Ueber die Bezieh. der Leber zum Kohlehydratstoffw. E. A. **33.** 305. 1894.
85. Garofalo: Über Glykosurie bei CO-Vergiftung und Leuchtgasvergift. Mo. U. **4.**
86. Weber: Ueber die Beeinfluss. des Stoffwech. durch einige pharm. wichtige Stoffe. Er. Ph. **3.** 2. 233. 1904.
87. von Noorden: Stoffwechsels. 1893. P. 316 ff.
88. Hoffmann: Ueber die Hippursäurebild. in der Niere. E. A. **7.** 233. 1877.
89. Araki: l. c., p. 452.
90. Katsuyama: Ueber den Einfl. einiger Gifte auf die Synthese der Phenolschwefelsäure. Z. p. C. **34.** 83. 1901.

2. Other Blood Poisons.

In this group are to be found a large number of bodies which differ considerably from one another in their chemical composition, but physiologically resemble one another in producing changes in the erythrocytes and hæmoglobin, thus interfering with the chemical and mechanical means whereby the oxygen supply to the tissues is maintained. The phenomena are due to partial deprivation of oxygen modified by the specific action of the various substances.

Many of these substances in quite small doses produce blood changes. In the case of poisoning by nitrites, chlorates, tannic acid, pyrogallol, arseniuretted hydrogen, and toluylendiamine, the symptom-complex is entirely dominated by this action. Others bring about the same result only in large doses or by the long-continued use of small doses; in this class belong many substances which will be dealt with later on—*e.g.*, bodies of the antipyrin, salicylic acid, and phenol groups, and substances like phosphorus, and many heavy metals, the other actions of which are more conspicuous.

We shall now deal briefly with those actions in which no distinction can be drawn between the effect on the blood-corpuscles and other special effects which accompany it.

Protein metabolism is increased by relatively small doses of chlorates (1), pyrogallol (2 to 4), pyrodin (5), toluylendiamine (2), and gallic acid (2); by toxic doses of bodies of the antipyrin class (aniline, para-amido-phenol, quinoline, hydrazine, and their derivatives), acetanilide (6), and thallin (7, 8). In the last group, as with salicyl and the heavy metals, it is impossible to say what part of the blood-changes brings about the protein decomposition. In the case of salicyl and the heavy metals (with the exception of mercury, perhaps, which has a severe destructive action on the erythrocytes), the breaking up of protein is part of a general toxic action on protoplasm.

The alkalinity of the blood is diminished. The cause of this is probably partly the acid nature of the decomposition products of the erythrocytes [lecithin (9)], and partly the deficiency in oxygen, with the consequent increase in protein decomposition and the production of acid bodies (lactic acid, etc.); the decreased alkalinity has been determined in the following instances by estimation of CO_2 and titration: nitrates (10), toluylendiamine, salicylic acid, cholalic acid, iodine and salts of hydriodic acid subcutaneously, pyrodin, glycerin, arseniuretted hydrogen, and pyrogallol (13, 28). The action of ether (subcutaneous injection) is very doubtful; the diminution in alkalinity observed by Kraus cannot be attributed to the action on the blood, and other observers have failed to note any such decrease (14).

In some cases, in spite of marked decrease in the oxygen content of the blood, there was a normal amount of carbonic acid, which may be looked on as adverse to the view that deficiency of oxygen is the cause of the fall in alkalinity. More careful analyses show that these findings must be grouped with exceptions of the following kind:

H. Meyer's Results.

	Volume CO_2.	*Volume O_2.*
	Per Cent.	Per Cent.
Cat, normal	27·0	14·0
Cat, NO_2-poisoning	18·1	2·4
Cat, toluylendiamine	25·2	5·2

The O_2 had diminished from one-seventh to one-third without any corresponding fall in CO_2. The explanation probably lies in the fact that the breathing became so inadequate shortly after the poisoning (both dogs died soon after the samples of blood were drawn) that the high percentage of CO_2 was due to a retention of the acid. We cannot conclude that there was necessarily a marked diminution of alkalinity to titration in these cases.

A rapid loss of glycogen was found after poisoning by amyl nitrite (15) and carbolic acid (16). Though this is not necessarily connected with its solution in the blood, we must regard it as a frequent occurrence when poisons act on the blood on account of the frequency of glycosuria dependent on hyperglycæmia.

Glycosuria has been also observed after chlorates (17 to 19), amyl nitrite (20 to 22), aniline (12, 23), nitrobenzol (24), and ortho-nitrophenol-propionic acid (25); probably in many other similar cases also. The cause has been but little investigated; we only know that it usually does not occur in starved animals, but whether—like the glycosuria of CO-poisoning—it depends on the nature of the food has not been determined. Lactic acid has been detected both in fasting and fed animals (rabbits and dogs) after poisoning by amyl nitrite. The neutral sulphur was found to be increased in pyrogallol poisoning (4).

In pyrogallol and toluylendiamine poisoning a remarkable increase

in chlorides has been observed in dogs poor in chlorine, as after CO-poisoning (26).

Decreased oxidation of benzol and decreased formation of hippuric acid have been noted after pyrogallol, and, in addition, decreased ethereal sulphates after amyl nitrite (27). In poisoning by the diamines there was decrease in the formation of hippuric acid, but not of glycuronic acid or the ethereal sulphates (1)—the latter were decreased in CO-poisoning (*vide supra*).

LITERATURE.

1. von Mering: Das chlorsaure Kali. 1885.
2. Noel Paton: The Relationship of Urea Formation to Bile Secretion. J. A. & P. **20.** 1886.
3. Kühnau: Ueber das Verhalt. des Stoffwech. und der weissen Blutelemente bei Blutdissolution. Ar. M. **58.** 339. 1897.
4. Bonanni: L'influenza del pirogallolo sui processi d'ossidazione e sintesi. Bu. R. **26.** 1900.
5. Fränkel: Ueber das Verhalten des Stoffwech. bei der Pyrodinvergiftung. Z. M. (Suppl.) **17.** 239. 1890.
6. Kumagawa: Ueber die Wirk. einiger antipyret. Mittel auf den Eiweissumsatz im Organismus. Ar. p. A. **113.** 134. 1888.
7. Livierato: Verhalt. des Stoffwech. unter dem Einfluss versch. antipyret. Substanzen. An. c. F. **3.** 322. 1885.
8. Maragliano: Über die biol. und therap. Wirk. des Thallin. Z. M. **10.** 402. 1886.
9. Kraus: Ueber die Alkaleszenz des Blutes und ihre Aenderung durch Zerfall der roten Blutkörperchen. E. A. **26.** 186. 1890.
10. Meyer: Über die Alkaleszenz des Blutes. E. A. **17.** 304. 1883.
11. Pohl: Synthesenhemmung durch Diamine. E. A. **41.** 97. 1898.
12. Jaffé: Zur Kenntnis der synthet. Vorgänge. Z. p. C. **2.** 47. 1878.
13. Fodera e Ragona: Influenza dell' asfissia delle sostanze che distruggono i globuli rossi e dell' ispessimento dell' saugue sulla sua alcaleszenza. A. F. **1898.** 1.
14. Thomas: Ueber die Wirk. einiger narkot. Stoffe auf die Blutgase, die Blutalkaleszenz und die roten Blutkörperchen. E. A. **41.** 1. 1898.
15. Konikoff: Ueber den Einfl. gewisser Agentien auf die Menge des Glykogen in der Leber. Ma. **6.** 198. 1876.
16. Bukowski: Veränderung des Glykogengeh. der Leber bei Karbolvergiftung. Diss. Würzb., 1894.
17. Falck: Beitr. zur Kenntnis der Chloratwirkung. Ar. P. M. **45.** 304. 1888.
18. Stokvis: Die Ursache der Giftwirk. der chlorsauren Salze. E. A. **21.** 169. 1886.
19. Cahn: Beitr. zur Kenntnis der Wirk. der chlorsauren Salze. E. A. **24.** 180. 1888.
20. Hoffmann: Beitr. zur Kenntnis der physiol. Wirk. des salpetrigsauren Amyloxyds. D. A. **1872.** 746.
21. Sebold: Ueber den Amylnitritdiabetes. Diss. Marburg, 1874.
22. Araki: Ueber die Bild. von Milchsäure und Glykose bei O_2-Mangel. Z. p. C. **15.** 546. 1891.
23. Brat: Ueber gewerbl. Vergiftungen und deren Behandlung mit Sauerstoffinhalation. D. m. W. **1901.** Pp. 296, 320.
24. Magnus-Levy: See Naunyn. Der Diabetes mellitus. **1898.** P. 31.
25. Hoppe-Seyler: Beitr. zur Kenntnis der indigobild. Substanzen im Harn und des künstl. Diabetes. Z. p. C. **7.** 403. 1883.
26. Kast: Ueber Beziehungen der Chloraussch. zum Gesamtstoffw. Z. p. C. **12.** 267. 1888.
27. Katsuyama: Ueber den Einfl. einiger Gifte auf die Synthese der Aetherschwefelsäure. Z. p. C. **34.** 83. 1901.
28. Kose: Über die alkal. Reaktion des Blutes. C. i. M. **1904.** 980.

B.—POISONS WHICH INDIRECTLY DISTURB THE RELATIONSHIP BETWEEN INTERNAL AND EXTERNAL RESPIRATION.

The poisons hitherto described act by changing the hæmoglobin, and so diminishing the absolute supply of oxygen to the tissues; others produce a deficiency of oxygen by disturbing the respiratory or circulatory apparatus which normally preserves a proper supply, or, leaving these intact, increase the requirements of the muscles to an extensive degree.

The deficiency in oxygen is thus indirectly produced, and it must be understood that no actual deficiency has been experimentally recognised; the similarity of the symptoms produced by direct deficiency has, however, led to the assumption that it exists. Hence it will easily be seen that in many cases it is difficult to decide whether poisons should be classed in this group, or in that subsequently to be described, in which the oxidizing power of the protoplasm is directly damaged. The experimental data, moreover, are too scanty to admit of the absolute exclusion of other factors in the production of the symptoms. For practical reasons we shall follow Hoppe-Seyler's (1) classification, without prejudice to the possibility of the occurrence of analogous symptoms due to O_2 deficiency.

Those which belong to this group are the narcotics, in doses sufficient to influence the respiration and eventually the circulation, especially morphine, ether, acetone, chloroform and curare in doses which paralyze respiration.

The specific action of curare not dependent on deficiency of oxygen will, with veratrine and cocaine, be dealt with in another place. It is questionable, in the case of both these poisons, whether they produce the group of symptoms shortly to be described actually and solely through inhibition of the respiration or circulation, or as the result of a direct action on the cells diminishing their oxidative capacity.

Protein metabolism is much increased both in starving and fed dogs by large toxic doses of morphine (2). Such doses should also decrease the alkalinity of the blood throughout this entire group of poisons, as, wherever it has been investigated, there has been a material increase of *lactic acid* in the blood (6). Estimations of CO_2 have been made in the case of strychnine[1] (3, 4) and morphine (5).

In poisoning by morphine, curare, veratrine, cocaine and strychnine (7) *sarcolactic acid* and *albumin* were regularly formed in the urine, whether the animals were starved or fed.

Glycosuria occurred after ether narcosis (8), inhalation of acetone (9 to 12), morphine-poisoning (13 to 19), strychnine-poisoning (14, 20 to 23), and veratrine and cocaine poisoning (14). The etiology of these conditions has not yet been determined.

The same thing is true in glycosuria after CO-poisoning, and after asphyxial conditions from various causes.

[1] A strikingly low proportion of oxygen in the blood was also found.

The very thoroughly investigated subject of curare glycosuria deserves special mention. It was discovered by Claude Bernard (25), who observed it apparently under conditions of unimpaired respiration. The view that it was not due purely to deficiency of oxygen (20, 26 to 29) is partly disproved by the fact that it was regularly absent under artificial respiration (30). Again, in curarized winter frogs, in which the O_2 absorbed by the skin is sufficient for the requirements of the organism, glycosuria was regularly absent (31). The fact that glycosuria appeared after quite small doses given by the mouth, and insufficient to produce paralysis, is no disproof (32). Possibly the usual kind of curare was not used, as careful subsequent experiments with various kinds of curare failed to confirm this result (28). Against the view that oxygen deficiency is the sole causative factor are the following observations : In one experiment the glycosuria was most irregular under apparently identical conditions (33), but this may have been due to individual differences in the O_2 requirements of the animals, naturally not applicable to the controls. On the other hand, active summer frogs, even under conditions of extreme privation of O_2, did not respond by glycosuria, though whether the muscles contained sugar was not determined (41, 42). A very important objection is the observation that frogs, even after the removal of the lungs, show no glycosuria (34).

Equally striking is the want of concordance in the results as to the significance of the glycogen content as a precursor of glycosuria. Glycosuria was observed in dogs after a week's fasting, but here glycogen may have been present (35). After the glycosuria the livers of frogs still contain a considerable store of glycogen (42), but this need not have been completely destroyed by the curare. Rabbits showed hyperglycæmia without glycosuria. On the other hand, glycosuria did not occur in animals poor in glycogen, and an enormous destruction of the latter has been observed under the influence of curare (37).

These contradictory results may be partly attributed to unreliable methods of estimating glycogen. Moreover, we know from results in CO-poisoning that not every kind of diet gives rise to glycosuria, and, finally, experiments on frogs are not absolutely comparable to those on mammals. We cannot, therefore, conclude with absolute certainty that glycosuria is not solely caused by dyspnœa ; it is probable that other concomitant causes cannot be excluded. It is interesting to note that there are but few poisons which do not occasionally give rise to sugar in the urine.

Ether and acetone glycosuria is more certainly due to deficiency of oxygen. Neither occurs if a sufficient oxygen supply is kept up ; similar glycosuria occurs with hydrogen (38), sulphuretted hydrogen (39), and nitrous oxide (40).

During starvation glycosuria occurs after poisoning with veratrine, cocaine, morphine, acetone, ether, and strychnine. The influence of food has been investigated in the case of morphine, but has given no certain results. In the case of ether, as with CO-poisoning, meat diet seemed to predispose to glycosuria, whereas carbohydrates did not.

Glycæmia as the proximate cause of glycosuria has been found in

the case of ether, acetone, and morphine; the glucose excretion follows the destruction of glycogen, as has been proved for strychnine, morphine, and other substances.

Probably the so-called transfusion glycosuria should be classed here, because the large amount of salt solution introduced with the blood dilutes it and produces a deficiency of oxyhæmoglobin (41).

The cause of the destruction of glycogen is as obscure as it is in CO-poisoning. It would be of value to know the amount of glycogen in the livers of well-fed animals in which poisoning has failed to produce glycosuria. It is not known whether it is decreased or not; in the former case it must be converted into some body other than sugar.

LITERATURE.

1. Hoppe-Seyler: Beitr. zur Kenntnis des Stoffw. bei Sauerstoffmangel. Festschr. f. Virchow. 1891.
2. Luzzatto: Ueber die Natur und die Ursachen der Morphiumglykosurie. E. A. **52.** 95. 1905.
3. Minkowski: Ueber den Kohlensäuregeh. des arteriellen Blutes beim Fieber. E. A. **19.** 209. 1885.
4. Kionka: Die Aenderung der Eigenwärme während der Strychninvergiftung. Arch. de pharmacodyn. **5.** 111. 1898.
5. Filehne u. Kionka: Ueber die Blutgase Normaler und Morphinisierter in Ruhe und Muskeltätigkeit, etc. Ar. P. M. **62.** 201. 1895.
6. Araki: Ueber die chem. Aenderungen der Lebensprozesse infolge von O_2-Mangel. Z. p. C. **19.** 422. 1894.
7. Araki: Ueber die Bild. von Milchsäure und Glykose bei O_2-Mangel. Z. p. C. **15.** 335. 1891.
8. Seelig: Ueber Aetherglykosurie und ihre Beeinflussung durch intravenöse Sauerstoffinfusionen. E. A. **52.** 481. 1905.
9. von Buhl: Ueber diabet. Koma. Z. B. **16.** 413. 1880.
10. von Jaksch: Epilepsia acetonurica. Z. M. **10.** 362. 1885.
11. Ruschhaupt: Ueber Azetonglykosurie. E. A. **44.** 127. 1900.
12. Müller: Ueber Azetonglykosurie. E. A. **46.** 61. 1901.
13. Eckhard: Ueber den Morphiumdiabetes. Eckhard's Beitr. **8.** 77. 1879.
14. Araki: l. c. (7), p. 546.
15. Adler: Ueber transit. Glykosurie bei einigen Fällen von akuter Morphium vergiftung. P. W. **25.** 327. 1900.
16. Lépine: Les glycosuries toxiques. Ar. m. ex. **15.** 129. 1903.
17. Luzzatto: Ueber die Natur und die Ursachen der Morphiumglykosurie. E. A. **52.** 95. 1905.
18. Bendix: Ueber aliment. Glykosurie nach Narkosen. C. S. **3.** 149. 1902.
19. Levinstein: Zur Pathol. der akuten Morphium- und Chloralvergiftung. B. k. W. **1875.** Nr. 27.
20. Schiff: Über die Zuckerbild. in der Leber und den Einfl. des Nervensyst. auf die Erzeugnisse des Diabetes. 1859.
21. Rosenbaum: Ueber den Kohlehydratbestand des tier. Organis. nach Vergift. mit Arsen, etc. Diss. Dorpat, 1879.
22. Gürtler: Der Strychnindiabetes. Diss. Königsb., 1886.
23. Langendorff: Über die Zuckerbild. in der Leber. D. A. **1886.** Suppl. 269.
24. Irisawa: Ueber die Milchsäure im Blut und Harn. Z. p. C. **17.** 340. 1893.
25. Claude Bernard: Leçons sur les effets des substances tox. et médicamenteuses. 1858.
26. Dieffenbach: Ueber die Existenz der glykogenen Funktion der Leber. Diss. Königsb., 1869.

27. Dastre: De la glycémie asphyxique. C. r. A. S. **89.** 669. 1879.
28. Zuntz: Ueber die Benutzung kurar. Tiere zu Stoffwechselunters. D. A. **1884.** 380.
29. Sauer: Ueber den sog. Kurarediab. und die angebl. Schutzwirk. der Leber gegen dieses Gift. Ar. P. M. **49.** 423. 1891.
30. Penzoldt u. Fleischer: Exper. Beitr. zur Path. des Stoffwechsels, etc. Ar. p. A. **87.** 241. 1882.
31. Winogradoff: Beitr. zur Lehre vom Diab. mell. Ar. p. A. **27.** 533. 1863.
32. Gaglio: Ueber die Wirk. der Kurare auf die Leber und die Ursache der Toleranz des Organismus, etc. Mo. U. **13.** 354. 1888.
33. Morishima: Ueber Harnsekret. und Glykosurie nach Vergift. mit Protokurarin und Kurarin. E. Ar. **42.** 28. 1899.
34. Langendorff: Zur Erklärung des Kurarediabetes. D. Ar. **1891.** 476.
35. Dock: Einfl. der Kurarevergift. auf die Glykogenbild. in der Leber. Ar. P. M. **5.** 501. 1872.
36. Luchsinger: Physiol. und Pathol. des Glykogens. Diss. Zürich, 1875.
37. Demant: Ueber den Einfl. des Strychnins und Kurare auf den Glykogengeh. der Leber und Muskeln. Z. p. C. **10.** 442. 1886.
38. Vamossy: Beitr zur. Kenntnis des Kohlenoxyddiab. E. A. **41.** 273. 1898.
39. Cahn: Akute Schwefelwasserstoffvergift. mit längerem Latenzstadium und sehr heftigen intest. Symptomen. Ar. M. **34.** 121. 1883.
40. Laffont: Infl. de l'Anesthésie par inhal. de protoxyde d'azote pur sur diverses fonctions de l'économie. C. r. A. S. **102.** 176. 1886.
41. Bock u. Hofmann: Über Diabetes. 1874.
42. Langendorff: Der Kurarediabetes. D. A. **1887.** 138.

C.—PRUSSIC ACID AND THE POISONS WHICH APPARENTLY INFLUENCE THE OXIDATIVE ACTIVITY OF THE CELLS.

Although symptoms of deficiency of oxygen are invariably produced by a deficiency in the oxygen supply of the cells, and especially as a secondary effect when the oxidative activity of the cells has been impaired by long deprivation, the poisons we shall now describe give rise to symptoms which exactly correspond to these without there being any obvious alteration in the amount or condition of the oxygen supply to the tissues. We must therefore assume some chemical change in the cells themselves which prevents their utilizing completely or partially the oxygen which is supplied to them in the normal manner. The result is naturally the same, namely, life without oxygen. This method of poisoning is only markedly seen in prussic acid, which we are about to describe; to a certain extent probably it occurs with the inorganic bodies phosphorus, arsenic, antimony. Similarly acting organic bodies are the halogen narcotics, oil of pennyroyal, cantharides, and possibly salicylic acid. The grouping of these bodies together must not be taken to mean that their often obscure actions are identical, but that a certain resemblance may be noted in the symptoms they produce.

1. Prussic Acid.

Our knowledge of the behaviour of the O_2 intake and CO_2 output during the different stages of poisoning by prussic acid in large doses

(1 milligramme per kilogramme) in rabbits, cats, and dogs is founded on the researches of Geppert.

In the first stages of poisoning there is a certain amount of restlessness, and the amount of O_2 inspired is somewhat increased (estimated partly by Zuntz's and partly by a modification of Regnault-Reiset's method).

Oxygen Consumption per Minute in c.c.[1]

Normal	21	28·8, 33·7, 33·1, 31·6	39·7, 39·3, 35·7, 42·1
During poisoning ..	26·7	46·4, 46·8	50·0, 65·0, 56·0

When the intoxication is more intense very different figures are obtained :

Oxygen Consumption and Volume of Respiration per Minute.

Normal	(512, 504, 458), 23·4, 21·9, 23·8			(395), 20·7	
During poisoning ..	(821, 518), 15·8, 17·4			(924, 551, 832), 5·0, 9·4, 9·1	
Normal	21·5	21	35·4	30·9	14·6
During poisoning ..	15·7	19·5, 15·1	21·2	19·8, 24·0, 28·9	12·3
Normal	29·3, 27·2, 28·8, 33·7		33·1, 31·6	39·7, 39·3, 35·7, 42·1	
During poisoning ..	16·0, 15·6, 21·6, 20·0		18·6	26·7, 21·7	

In this stage the O_2 consumption is regularly and markedly decreased ; the animals, however, are more restless than normal, and the change from the higher to the lower figures cannot be recognised by observing their behaviour. When the poisoning is temporary, and the animal recovers, the figures during the stage of recovery usually rise again before settling down to normal. The following table gives a clear picture of the course of events during the various stages :

O_2 Consumption per Minute in c.c.

Number of Experiment.	*Normal.*	*Poisoned.*		*Return to Normal.*	*After the Poison is Removed.*	*Animal.*
		First Period.	Second Period.			
8	22·7	—	15·8–17·4	—	23·8	Rabbit.
11	20·7	—	5·0–9·4	—	—	Rabbit.
21	35·4	40·20	21·2–19·8–24·8	—	30·9	Cat.
22	30·9	60·40	24·0–28·9	44·8	—	Cat.
25	28·8	46·40	16·0–20·0	30·5–30·8	33·7	Cat.
27	39·7	80–52	26·1	60·6–53·2	39·3	Dog.
28	35·7	65–46	21·7	36·6–52·0	42·1	Dog.

When the poisoning is more severe, a second stage supervenes, characterized by severe spasms, which in a normal animal would produce a marked rise in the consumption of O_2. In poisoned animals, however, dogs alone show any such rise, and then only at the beginning of the spasms. Otherwise there is only a diminution of O_2 consumption.

[1] The figures above and below the lines apply to the same animal in one or more experiments. The bracketed figures indicate volume of respiration.

O_2 Consumption and Volume of Respiration per Minute.

	Rabbit.	*Rabbit.*	*Dog.*
Normal	(524, 483)	(415)	(1,240, 1,200, 1,400)
	20·8, 19·0	16·1	65·4, 63·2, 61·0
During spasms ..	13·6	6·1	71·9
	(857)	(1,041)	(6,600)

	Dog.	*Dog.*	*Dog.*	*Dog.*
Normal	(1,676, 1,598, 1,711)	(1,605)	(1,123)	(1,241, 1,371)
	104·0, 94·0, 105·0	73·0	57·0	60·0, 64·0
During spasms ..	116·0	44·6	36·0	39·0
	(11,150)	(6,033)	(6,870)	(6,758)

	Rabbit.	*Dog.*	*Rabbit.*	*Rabbit.*
Normal	(321)	(992)	—	—
	15·1	62·0	21·5, 21·0	28·0
During spasms ..	11·3	54·0	12·8, 10·2	19·0
	(1,252)	(7,166)	—	—

	Cat.
Normal	33·1, 31·6, 29·3, 27·2
During spasms ..	13·0, 23·3

In nearly all cases the O_2 consumption is markedly diminished in spite of severe convulsions.

In order to confirm still more this very remarkable result, Geppert tetanized normal and poisoned animals to the same degree and for the same length of time. Estimations of the oxygen intake showed that in all cases it was below normal in the poisoned animals, often below that for normal non-tetanized animals. The oxidation process was calculated at two-thirds to four-fifths less than normal.

During the paralysis following the spasms the O_2 intake often rises, apparently owing to the fact that the action of the prussic acid by this time is beginning to pass off.

The symptoms are the same when the poison is administered subcutaneously or intravenously.

From these experiments we may conclude that the action of prussic acid is to decrease oxidation processes in the animal body.

The estimation of the amount of CO_2 found is, of course, of much importance for determining the nature of the changes on which the motor phenomena depend. This, however, cannot be directly determined, the amount of CO_2 excreted—which alone can be estimated—is not the sole result of CO_2 formation. It is more possible to estimate the latter by the activity of the respiration and the alkalinity of the blood. Both these factors influence the CO_2 content of the blood in the same direction; increased respiration and alkalescence both produce a fall.

The first table on p. 1102 gives Geppert's results.

The CO_2 in arterial blood sinks remarkably during the intoxication (eventually to about half its orginal amount), and under the circumstances the fall is very rapid (36).

CO_2 IN C.C. IN 100 C.C. BLOOD.

Number of Experiment.	*Normal Animals.*		*Poisoned Animals.*		*Remarks.*
	Arterial.	Venous.	Arterial.	Venous.	
34	41·1	—	22·0	48·2	Dog; arterial in first spasm; venous during paralysis.
35	43·7	—	18·0	—	Dog; severe spasms.
36	40·3	—	23·6	—	Rabbit; six minutes after injection.
33	—	50·3	17·7	—	Rabbit; after spasms.
37	41·4	—	23·9	30·2	Rabbit; venous at end of spasms; arterial during paralysis.
29	—	—	—	35·3	Rabbit; venous (1) at beginning of poisoning; arterial eleven minutes after.
			7·7	17·0	Spasms; venous (2) thirty minutes after spasms.
38	36·0	46·2	11·0	33·1	Dog; severe poisoning; venous two minutes after arterial.
39	44·8	—	27·6	—	Rabbit; at beginning of spasms.

The CO_2 content of venous blood sinks to below the usual figure for arterial. This fall in the blood content explains how during intoxication the CO_2 output increases in proportion to the intake of O_2.

EXCRETION OF CO_2 IN C.C. FOR EVERY 100 C.C. O_2.

Number of Experiment.	*Animal.*	*Normal.*	*Poisoned in Various Stages.*				
			First Stage (slight, after Rigors).		Normal, after Three Hours.	Second Stage (Spasms).	Paralysis.
4	Rabbit	90	130, 93, 82		70	92	94, 89, 64
			First Stage (no Spasms).				
8	Rabbit	86	131, 92, 80		—	—	—
			Fir·t Stage.	Spasms.	Paralysis.	Beginning of Movement.	Normal.
9	Dog	72	111	89, 145	112, 134	67	71
10	Dog	70	98	115	97, 98	81	61, 69

As the respiration is always increased, we must attribute some of the fall in the CO_2 content of the blood and its increase in expired air to this circumstance. Geppert does not regard this as the sole cause—

1. Because the CO_2 excretion reaches normal so slowly.
2. Because in experiment No. 8 in a slightly poisoned animal which

had no spasms, in which the amount of air expired was normal (518 as against 512 normal), for every 100 c.c. of inspired O_2, 92 c.c. CO_2 (as against 86 c.c. normal) was excreted. The difference is small.

Geppert also concluded that the alkalinity of the blood must be diminished, which is highly probable when one remembers that it falls owing to insufficient oxygenation of the tissues. For this it is of no consequence whether the insufficiency arises from a diminished supply (as in CO-poisoning), or in a diminished power in the tissues to use it. That spasms are the only cause is, moreover, shown by the facts that the CO diminishes in the blood before they set in, and the increase in acidity after the spasms is only the result of a relative want of oxygen.

The question next arises as to whether there is increased formation of CO_2. Geppert found that if the poisoning is sufficiently severe to diminish the consumption of O_2 to below normal, the CO_2 output will at most be at the normal, or may fall a little below it. Frequently it remains below. Hence the amount of CO_2 formed must be far below the usual amount for the resting condition, for, in calculating the amount formed from that excreted, a large deduction must be made corresponding in amount to the quantity previously stored in the body and excreted during the intoxication, owing to the heightened alkalinity and increased respiratory movements. When it is remembered that, under normal conditions, the CO_2 output is much increased during muscular work, it follows that the decrease in formation during prussic acid poisoning must be considerable. This decrease, too, does not appear to vary with the decrease in the amount of O_2 used; when this did not sink below normal the excretion of CO_2 rose above it.

Geppert controlled his results by a comparison of the CO_2 output in normal and poisoned animals when tetanized.

CO_2 Excretion in Tetanization.

Number of Experiment.	*Normal.*	*Poisoned.*	*Remarks.*
7	355	99	Severe spasms; dog.
12	26	9	Severe spasms; rabbit.
14	291	169	Slight spasms; dog.
—	—	117	Severe spasms.
16	132	74	Spasms; dog.

Conclusion.—CO_2 formation and O_2 absorption are simultaneously and equally diminished. The diminution in CO_2 formation is apparently due to the fall in oxygen absorption.

(*a*) *The Cause of the Diminution in Oxidation Processes.*

A priori two possible causes may be considered: (1) Either the blood is so changed by the HCN that its O_2 cannot be utilized by the tissues, or cannot be completely utilized; or (2) the blood is not changed, but the tissues have lost the power of using the O_2 of the normal hæmoglobin.

Oxyhæmoglobin forms with HCN a very stable compound, but this probably does not take place within undamaged erythrocytes. That this compound is not the cause of the bright red venous blood of animals poisoned by HCN is shown by the fact that the toxic dose is too small to produce sufficient CN methæmoglobin. The question therefore arises as to the possibility of some other blood change which could be held accountable. It must be something which renders it difficult for the blood to part with its O_2. Against such a change occurring stand the facts that cold-blooded animals which possess no hæmoglobin are equally affected by the poison, and that if the blood is withdrawn during the paralytic stage it becomes dark as rapidly as that of an unpoisoned animal. Again, Geppert has shown that the red colour of the venous blood is actually due to the high O_2 content.

Percentage of O_2.

Number of Experiment.	*Arterial.*	*Venous.*	*Difference.*	*Animal.*
30	12·2	10·9	1·3	Rabbit.
31	13·0	12·4	0·6	Rabbit.

So slight a difference in O_2 content between arterial and venous blood does not normally occur, and the proportion of O_2 is high enough to account for the bright red colour. Moreover, Geppert showed that by inspiring an atmosphere poor in O_2 the bright red blood of poisoned animals in forty seconds becomes dark, and that the O_2 is easily withdrawn. Lastly, he proved that there is no diminution in the power of the hæmoglobin to unite with oyxgen.

Thus it has been indubitably shown that the poisoning produces no change in the oxygen compound in the blood.

The tissues, therefore, must be the seat of the toxic process, and must have lost the power of using the O_2 brought there. "Prussic acid poisoning is an internal asphyxia of the organs in the presence of an excess of oxygen" (Geppert).

Prussic acid can produce similar action *in vitro—e.g.*, it can prevent formic acid from parting with its oxygen to hydriodic acid. The character of this action of HCN must be left undecided. As illustrations may be mentioned its power of stopping anaerobic processes, like the alcoholic fermentation of sugar by zymase; the action of the tissue oxydases is inhibited (just as in the H_2O_2 catalysis by platinum) with a dilution of 1 in 700,000,000 HCN. In all these processes a "recovery" is possible.

The most interesting result of the investigations is the very well established fact that the spasms occur not only when there is diminished consumption of O_2, but diminished formation of CO_2. It is known that a muscle can go on working for a long time with a decreased O_2 supply; it can in this case use up the reserve O_2 and form CO_2. Pflüger (2) has

actually shown that in an atmosphere free from O_2 cold-blooded animals will form and excrete an undiminished amount of CO_2 for a long time. But in HCN poisoning the power of using up reserve O_2 is conspicuously absent; at any rate, during the convulsions the CO_2 formation is not only not raised, but falls considerably below the normal amount. The muscle can contract without using O_2, and this may be recognised in these cases of poisoning exclusively. "The power to combine with O_2 appears to be a property of muscle which is both activating and paralyzing" (Geppert.) The heat produced might well arise from hydrolytic processes, also anaerobic, without the formation of CO_2 as an end-product.

(*b*) *Other Metabolic Changes.*

On this subject there are at present no experimental data. It is certain, however, that important changes take place, and mainly when the process is not gradual (*cf.* deprivation of oxygen); the nature of the processes will be the same whether the O_2 consumption by the cells is disturbed through their inability to use it when brought to them, or by its not being brought to them at all, with this distinction, however—that in HCN-poisoning there is in addition an inability to use the intracellular oxygen. Thus a comparison of the symptoms shows a close analogy between HCN-poisoning and total deprivation of oxygen.

Quite recently it has been shown that in dogs poisoned by zinc cyanide the protein metabolism and the excretion of amino-acids is much increased (3). Lactic acid has been found in the blood and urine (4). Glycosuria was not found in one case (4), but was observed in another (5) (potassium zinc cyanide).

LITERATURE.

1. Geppert: Ueber das Wesen der Blausäurevergiftung. Berlin, 1889. Hirschwald.
2. Oertmann: Ueber den Stoffwechsel entbluteter Frösche. Ar. P. M. **15.** 381. 1877.
3. A. Loewy: Bemerkungen über experimentelle Störungen des Eiweissabbaues. C. P. **19.** Nr. 23. 1906.
4. Zillessen: Ueber die Bildung von Milchsäure und Glykose in den Organen bei gestörter Zirkulation und bei der Blausäurevergiftung. Z. p. C. **15.** 387. 1891.
5. Frerichs: Ueber den Diabetes. Berlin, 1884. 30. Hirschwald.
6. Cl. Bernard: Leçons sur les effets des substances toxiques et médicamenteuses. Paris, 1857.

2. Poisons which probably Decrease the Oxidative Activity of the Cells.

(*a*) *Phosphorus, Oleum Pulegii, Halogen Narcotics of the Fatty Series' Arsenic, Antimony, and Iron.*

Gaseous Metabolism.

Phosphorus.—Gaseous metabolism during phosphorus-poisoning in warm- and cold-blooded animals has been repeatedly investigated, but

under such conditions that from the results alone we can form no clear conception of the general influence on general metabolism.

This holds good for the early experiments of T. Bauer (1), so often quoted. The CO_2 output was estimated by Pettenkofer's apparatus on the second and third day of starvation in a dog, and four days later after the subcutaneous administration of very large amounts of phosphorus.

	First Day (Normal).	*Second Day (Normal).*	*Third Day (Poisoned).*
Water	6·86	5·95	4·31
CO_2 in c.c. per minute ..	13·50	9·51	5·04
O_2 in c.c. per minute	11·36	8·11	4·50
Respiratory quotient.. ..	1·20	1·10	1·10

The fall was not, apparently, so great after three days' starvation as after the phosphorus, which Bauer therefore referred to the poisoning. With this we agree, but do not consider it justifiable to draw conclusions from this with regard to the specific action of phosphorus, because at the end of the estimation of the respiration—thirty-six hours after the first administration of phosphorus—the dog died. These figures, therefore, must be considered as obtained *in extremis*, and due to the cessation of the vital processes. Others have observed no alteration in the gaseous interchange in mice under phosphorus-poisoning (2), but results in such animals must, of course, be received with much reserve. With a very primitive method Scheider carried out three experiments (3), the most important of which may now be cited.

CO_2 excretion in rabbit weighing 797 grammes during two hours :

Normal diet	2·7090 grammes.
After one day's fast	2·2743 ,,
After two days' fast	2·1094 ,,

The animal was fed up till its weight was 842 grammes :

After its last meal it excreted	2·6198 grammes.
One and a half days after poisoning with 13 mgm. phosphorus *per os* it excreted	1·4838 ,,

—about 26 per cent. less than during fasting alone on the second day. It is impossible that the reduction in CO_2 values obtained on the day of experiment should, in the absence of direct information, be referred to loss of body-weight, nor is it likely that a loss of weight could cause such a marked fall in CO_2. This experiment seems to show that phosphorus-poisoning decreases oxidation processes more than hunger alone.

Recently Welsch (5) has investigated the subject in dogs and rabbits. In his seven experiments the O_2 intake and CO_2 output decreased about 11 per cent. to 20 per cent. of the normal. Calorimetric experiments by the same author on rabbits (d'Arsonval's apparatus as modified by Frédéricq) showed a decrease in oxidation.

Exact observations have been made on winter frogs by means of Pflüger's modification of Regnault and Reiset's apparatus (4). The experiments lasted for from eleven to twenty-four hours. The gaseous metabolism was determined before and during poisoning in the same groups of animals. The results varied widely. In four experiments the poisoned animals took more O_2, and in three less; in two they excreted more, and in five less, CO_2 than the unpoisoned frogs. The respiratory quotient in four was greater, in two about the same, and one less. The conclusion that phosphorus increases the total exchange cannot be considered proved by these experiments on cold-blooded animals.

Fat Metabolism.

Many more attempts have been made to obtain an insight into the primary disturbances by estimating the quantitative changes in the fat and carbohydrate content of the body under the influence of the poison. Unfortunately, the results have not been checked by the use of control animals, so that there is always the possibility of uncontrollable error.

Experiments with Warm-blooded Animals.

Two guinea-pigs from the same litter were starved for five days; one was then poisoned (per rectum), and when it died the other was killed and both animals analyzed (6).

	Control Animal.	*Phosphorus-poisoned Animal.*
	Gm.	Gm.
Fresh weight (without stomach and intestines)	210·00	231·00
Dry weight	65·80	68·86
Weight of ethereal extract:		
(*a*) Absolute	6·37	13·37
(*b*) Per cent. fresh weight	3·03	5·80
(*c*) Per cent. dry weight	9·60	19·40

In the phosphorus animal there was considerably more fat than in the normal. Unless it was previously present this excess of fat must have been either newly formed or have escaped oxidation. To elucidate this point a second experiment was made on two rats; one was killed after five days' starvation to determine the orginal amount of fat, and phosphorus was given to the other one.

If we assume that the excretion of fat was the same in both animals, we must conclude from the experiment that, contrary to the first experiment, during the poisoning by phosphorus there was no excess of fat formed, or that it was masked by increased consumption. In order to reconcile this result with that of the first experiment, we must conclude

that there is no absolute increase in fat formation, but that in animals poisoned by phosphorus there is a diminished consumption.

	Control Animal.	*Phosphorus-poisoned Animal.*
	Gm.	Gm.
Weight at death	171·70	123·70
Dry weight	54·17	42·10
Weight of ethereal extract:		
(*a*) Absolute	6·55	3·30
(*b*) Per cent. fresh weight	3·81	2·66
(*c*) Per cent. dry weight	12·00	7·80

But it is not possible to reconcile the results of the two experiments, as the excretion of fat was probably very different. Experiments on four pigeons, of which two were from one brood, showed (7):

	Unpoisoned.[1]	*Poisoned.*		
	Pigeon 1.	Pigeon 2.	Pigeon 3.[2]	Pigeon 4.
	Gm.	Gm.	Gm.	Gm.
Weight at death	214·00	216·000	159·00	217·000
Weight of fat:				
(*a*) Absolute	8·38	3·844	3·38	7·594
(*b*) Per cent.	3·90	1·800	2·10	3·500

Unless one makes the quite improbable assumption that within two hours the third pigeon lost the greater part of its fat, we see by a comparison of this with the control bird how much the fat excretion varies. As bird No. 4 lost about the same amount as the control, it cannot be concluded that phosphorus diminishes the fat content of animals.

On the strength of a single experiment Bergeat assumes that phosphorus produces a new formation of fat (8).

The amount of fat has been compared in poisoned and unpoisoned mice, all of which were copiously fed with bacon (9). The unpoisoned showed 14·2 to 29·3 per cent., and the poisoned 4·13 to 7·9 per cent. of fat at death. From these figures we may conclude that after poisoning the animals freely split up fats, but not that they do so more or less than starved unpoisoned animals, or that a new formation of fat has partly concealed the loss.

Experiments with Cold-blooded Animals.

In Leo's experiments on eighteen frogs it is not stated whether the animals were of the same or different sexes—a point of great importance with regard to the amount of fat present (6).

[1] Starved till the death of the last of the poisoned pigeons.
[2] Death two hours after poisoning.

	Six Animals of Equal Size.	*Twelve Animals Killed at the Same Time.*	
		Six Poisoned by Phosphorus.	Six Normal.
	Gm.	Gm.	Gm.
Fresh weight ..	252·000	260·000[1]	228·000[1]
Dry weight	57·065	60·656	53·163
Ethereal extract ..	5·297	6·131	5·148
Lecithin	1·860	1·960	1·900
Per cent. fresh weight (ether extract) ..	1·360	1·600	1·420
Per cent. dry weight (ether extract) ..	6·020	6·710	6·100

It is not possible to conclude from this that fat is newly formed in animals poisoned by phosphorus, as in frogs the amount varies enormously; two groups are often entirely different from one another, as the following table shows :

Number of Experiment.	*Dry Substance.*	*Fat.*	
		Fresh Weight.	Dry Weight.
	Per Cent.	Per Cent.	Per Cent.
1	19·33	1·47	7·64
2	19·96	0·85	4·27
3	20·57	0·77	3·78
4	20·92	1·38	6·68

An attempt was made to exclude this variable fat content by extirpating the fat bodies and the generative organs (10); but the fat and the dry weight varied in normal animals between 18·99 to 24·9, and the fat percentage of dry weight between 3·8 and 6·5. Further possible sources of error have also been pointed out in this research (11), so that we cannot conclude from it that there is any new formation of fat in phosphorus-poisoning. From numerous experiments on frogs, Athanasiu came to the conclusion that the absolute amount of fat in the body was not altered by the influence of phosphorus (4).

Finally, Taylor (12) experimented on *Rana palustris* under circumstances that amply ensured a correct basis for comparison. Twenty-eight animals were kept in a warm chamber for a long time in order to ensure as far as possible freedom from fat and glycogen. Fourteen were taken as controls, and fourteen animals, weighing the same as the controls, were given large doses of phosphorus. As soon as a poisoned animal died, the corresponding control was killed, and those surviving twelve days after poisoning were killed at the same time.

[1] From the time of poisoning till the moment of death the poisoned animals had not lost more, but exactly the same amount as the controls.

	Fourteen Controls.	*Fourteen Phosphorus-poisoned Animals.*
	Gm.	Gm.
Original weight	294·430	294·35
At death	277·700	302·10[1]
Dry weight	48·855	44·62
Percentage of original weight ..	18·150	15·15

The phosphorus animals had lost rather more :

	Gm.	Gm.
Ethereal extract after digestion	4·534	3·508

The phosphorus animals had lost about 22 per cent. more :

	Gm.	Gm.
Fat	3·904=86·1 per cent.	2·968=84·6 per cent.
Lecithin ..	0·630	0·540

From these results we may conclude that there is marked breaking down of fat in phosphorus-poisoning.

From these numerous experiments no certain conclusions as to the general metabolism of fat are permissible; a new fat formation may be excluded. That metabolism is decreased—at any rate, in warm-blooded animals—and fat-splitting processes are diminished is highly probable.

Carbohydrate Metabolism.

Salkowski's observation that, especially in young animals, glycogen disappears rapidly from the liver in phosphorus-poisoning, has been frequently confirmed (5, 15, 16). Of itself this implies no specific action on the part of the phosphorus, as the animals took hardly any food after being poisoned, and starved animals also lose their glycogen very rapidly. Comparative experiments are, therefore, very important to check these results (18, 19). In frogs for every 100 grammes body-weight there was 0·093 gramme less glycogen in the phosphorus-poisoned animals than in the controls; the smaller the figure in itself, the more conclusive it is when found true of a large number of animals. In rabbits a smaller amount of glycogen was regularly found in the livers of the poisoned animals than that in the normal animals which had been starved equally long. In white rats a similar difference was always found, but not always so great.

Not only was the glycogen in the liver estimated, but also that in the rest of the body, which was important with a view to ascertaining whether there was an actual consumption of the liver glycogen, or whether, as seemed more probable, it was only removed to another place. Finally, also, the entire carbohydrate content of the animal was determined. The constant result was that the greatest decrease in the glycogen

[1] Increase due to œdema. Phosphorus is a "capillary" poison [Magnus (13)].

content of the phosphorus animals was found in the liver, but that the amount in the rest of the body, as well as the total carbohydrates, were also decreased throughout.

It has already been established that muscle glycogen is more resistant to phosphorus-poisoning than that in the liver. Generally, therefore, we may conclude from these experiments that in phosphorus-poisoning there is an increase in carbohydrate metabolism.

Still, it is possible that, besides this increased consumption, the poisoning causes a decreased production of carbohydrate, such as normally takes place during starvation (20 to 24). This assumption has been made on the strength of the observation that the fatty phosphorus liver was not favourably affected by carbohydrates (25). Experiments, however, have shown that in rabbits which have been starved for some time after the administration of phosphorus for three days—in winter, at any rate—considerable amounts of glycogen can be detected in the liver as long as there is a good intake of grape-sugar (17). Hence it is probable that the animals have not entirely lost the power of forming glycogen.

How is it, then, in presence of the rapid destruction of glycogen so insisted on by some authors, that sugar seldom or never passes into the urine? The following are the facts. In the first place, all observers are agreed that glycosuria is a relatively infrequent event in phosphorus-poisoning (26 to 32). In 141 cases of phosphorus-poisoning in the Prague Medical Clinic glycosuria occurred in six cases, and in only four of these during the first week. From this no facts could be established as to the most usual determining condition—*e.g.*, severity, etc. In animal experiments glycosuria never occurred. In other cases of poisoning in which there was a rapid destruction of glycogen [curare, strychnine, caffeine, deprivation of oxygen (33)] glycosuria was very frequent in fed animals; it is determined by a previous hyperglycæmia, caused by direct destruction owing to chemical or nervous interference with the liver. As, then, this is so infrequent in phosphorus-poisoning, there must be some other cause for the destruction of glycogen. Some light may be shed on the question by investigating the sugar in the blood. The only figures available are those of Kaufholz. In normal animals he found 0·04 to 0·121 per cent. glucose in the blood; in poisoned animals, 0·147, 0·244, 0·249 per cent. In one case no glucose was present, and in another there was 0·68 per cent.; the last two figures are so unusual and improbable that perhaps these results are not quite trustworthy. Neubauer (17), after preliminary experiments in order to test the methods, adopted those of Pflüger and Allihn. In two poisoned animals, which had received grape-sugar before and after the dose of phosphorus, the amount in the blood was from 0·11 to 0·13 per cent.; these quantities are not sufficient to cause an excretion in the urine.

In three of Kaufholz's experiments the figures were within the limits of the normal sugar content of the blood.

The absence of glycosuria is not remarkable in view of these results. Though the glycogen is rapidly destroyed, it is only occasionally that the rapidity is enough to overload the blood with sugar. We must, therefore, seek for other causes for the glycogen destruction than those

obtaining in other kinds of poisoning or in the diabetic puncture. Possibly sugar is produced in such quantities as can be immediately used up, in which case we must assume that the cause of the disappearance of the glycogen is an increased demand for sugar. Then cases in which glycosuria occurs would be explained as due to overaction by the liver in destroying glycogen. Analogous processes occur; in fevers May (36) has clearly demonstrated this by experiment. It is not certain in either case whether the primary cause is a relative disturbance in the fat consumption. Investigations by Baldi (37) and Graham Lusk (38) gave no decisive results upon this point. There is, however, a second possibility —namely, that immediately after poisoning the glycogen or the sugar derived from it is partly, or completely, converted into lactic acid. This has been shown to be a very probable occurrence in arsenical poisoning (128). When the liver is freed from glycogen and then transfused with blood poor in sugar little or no lactic acid is produced, whereas if the liver is rich in glycogen large quantities of lactic acid are obtained (146). Lactic acid may also be obtained from the blood and urine after injections of phlorizin, and occasionally after injections of sugar (129).

This appears to be a reversible action, as under certain circumstances lactic acid becomes sugar (34).

In cases of poisoning the power of assimilating sugar often appears to be somewhat decreased; at any rate, Lamb met with alimentary glycosuria in 50 per cent. and Walko in 68 per cent. of their cases. Frerichs and Münzer (39) did not find this condition, and Welsch, in his phosphorus-poisoned rabbits, injected considerable amounts of glucose subcutaneously (2 grammes per kilogramme) without causing glycosuria.

Local Alterations in the Fat Content of the Body.

Quantitative Changes in the Content of the Ethereal Extract of the Organs.

Although the metabolism of fat is, as we have seen, apparently decreased, it has been clearly shown that the fat content of certain organs is regularly increased at the expense of that of others during poisoning by phosphorus. This increase is absolute, and has been shown by comparing the ethereal extracts in normal and poisoned men and animals. The greatest increase takes place in the liver, the next in the heart; that in the kidneys is exceedingly doubtful. A chemical and not merely a microscopical examination is necessary, for we know that an organ may appear extensively infiltrated with fat microscopically without the least real increase in its fat content. It is not understood how it is that the fat becomes so visible in these cases. The suggestion has been made that in infectious and other conditions cloudy swelling and processes leading to cell degeneration occur, and that thus a special reconstitution of the protoplasm takes place whereby fat or fatty bodies become apparent. This may be due to an acidosis, as acidification is the usual histological method of making fat visible. Researches on the human subject are dealt with in (40) and (41), on animals in (42) and (43).

The following table makes it possible to compare the fat content in the livers of normal men and those poisoned with phosphorus :

Condition.	*Ethereal Extract in Fresh Liver.*	*Amount of Water in Fresh Liver.*	*Author.*
	Per Cent.	Per Cent.	
Normal	3·46	79·6	Heffter.
	3·28	68·4	
	3·00	76·1	Von Starck.
	2·80	—	Kraus and Sommer.
	3·60	—	
Phosphorus	32·20 (1)	56·5 (1)	R. von Hösslin (64).
	29·80 (2)	60·0 (2)	Von Starck.
	23·30 (5)	61·0 (3)	
	25·40 (4)	62·2 (4)	Heffter.
	26·70 (3)	64·4 (5)	Von Starck.
	22·90 (6)	66·4 (6)	Heffter.
	19·50 (7)	67·9 (7)	
	37·50	—	Kraus and Sommer.
	37·70	—	

The figures in brackets show the fall in the fat content serially, and the corresponding rise in the amount of water. The general correspondence between the two shows that the fat is not a mere addition to the liver, but takes the place of water (63).

An increase in the fat content of the heart in man and animals has been shown by Krehl and others (45, 46). In the muscles in two cases of phosphorus-poisoning 15·1 to 19·5 per cent. fat calculated for the dry substance was found—a considerable increase above the normal.

As regards the kidney the results are not uniform : in a large series of experiments there was no increase, but in a single case in a man a large increase was noted. In the experimental animals, prior to the administration of phosphorus, one kidney was removed for comparison [Rubow and Rosenfeld].

Condition.	*Dry Substance in Right Kidney (Unpoisoned).*		*Dry Substance in Left Kidney (Poisoned).*	
	Ethereal Extract.	Lecithin.	Ethereal Extract.	Lecithin.
	Per Cent.	Per Cent.	Per Cent.	Per Cent.
Dog: normal	13·80	—	13·60	—
	15·20	—	14·90	—
	19·46	(6·6)	21·28	(6·8)
	14·00	(8·6)	14·90	(8·6)
Dog: starved	8·60	—	8·60	—
Dog: phosphorus	13·60	(7·8)	13·10	(7·1)
	15·60	(8·5)	15·80	(8·3)

Quantitative Composition of the Ethereal Extract.

The figures quoted hitherto have referred to the total fat of the ethereal extracts. But, in order to determine whether the increase is due to fat or fatty bodies, such as lecithin, protagon, etc., qualitative analyses must be made. This is all the more important in that Heffter, as the result of numerous careful analyses, found that 75 per cent. at least, and occasionally 99 per cent., of the ethereal extract of normal rabbits' livers consisted of lecithin. In Lee and Taylor's work the non-fatty substances were calculated; in that of Krehl, Athanasiu, Carbone and Heffter the lecithin was determined directly.

Leo found no change in the non-fatty matter of the ethereal extract of the whole animal, although the total amount of the extract was decreased. Heffter states that the figures are unreliable because the extract was heated to 100° C. (which would decompose the lecithin). Athanasiu obtained like results in frogs by a more delicate method. His figures showed 17·7 per cent. of total fat as lecithin in poisoned frogs and 18·0 per cent. in the normal. The total fat was also unaltered. Taylor showed a slight decrease in the non-fatty portion of the extract of the whole animal.

	Normal.	*Phosphorus.*
	Per Cent.	Per Cent.
Fat in ethereal extract	86·10	84·60
Residue in ethereal extract	13·90	15·40
Residue, absolute amount	0·63	0·54

In warm-blooded animals (dogs) Carbone obtained the following figures (a piece of liver was removed for comparison before the poisoning):

	Before.	*After.*
	Per Cent.	Per Cent.
Total ethereal extract in fresh liver	1·85	2·75
Total lecithin extract in fresh liver	2·29	1·49

The animal was given large doses of phosphorus. In other cases with small doses the lecithin was increased. Heffter obtained similar results: as against 2·2 to 3·07 per cent. lecithin in healthy rabbits, in poisoned animals it fell to 1·1 per cent., or in absolute amounts from 1·8 to 0·88 gramme. In men the findings are the same: normally the lecithin is 2·1 per cent.; after phosphorus-poisoning it was 1·56 per cent. On the other hand, Lusena found 1·6 per cent. in the healthy liver, and 1·9 per cent. in the liver, 2·0 per cent. and 1·85 per cent. in the kidney, and 1·58 per cent. and 1·77 per cent. in the heart, of the poisoned

animals (47). Bonanni did not find any marked change in very acute poisoning (48).

With regard to the composition of the ethereal extract of the heart, in the case of a man Krehl found no more than the normal amount of lecithin (the absolute figure is sufficiently constant normally to allow of a comparison), though the ethereal extract was larger than normal. Thus simple fat alone had increased. Rubow found—

Heart (Percentage of Dry Substance).

	Ethereal Extract.	*Lecithin.*	*Fat.*
Normal dog ..	12·60	8·3[1]	4·30
Starved dog ..	11·18	7·5	3·69
Poisoned dog ..	11–20	7·9–8·9	3–11

The lecithin in the kidneys remained unaltered.

General Conclusions.—The liver and the heart, but not the kidneys, become richer in fat. The lecithin in the liver is absolutely and relatively decreased, but that in the heart is increased according to the total increase in fat ; in the kidneys there is no change.

The Cause of the Increased Fat in Liver and Heart.

A greater part of the interest which has been taken in the phenomena of phosphorus-poisoning is due to the endeavour to obtain some information as to the origin of fat, and especially as to the possibility of its arising from protein. As we are not here concerned with the historical aspect of modern problems, we must be content with a short résumé of this interesting controversy. The fat which we find in increased amounts in certain organs after poisoning by phosphorus does not arise on the spot, but is transferred from other parts of the body. The following experimental results support this view :[2]

1. Determinations of the ratio between the total body-fat and that in the organs (49 to 51).

2. Feeding experiments with fats not found in the body (50).

3. Researches on the chemical constitution of the fat in the fatty organs (50).

4. Determination of the amount of fat in lymph and blood (52, 53).

Leisering was the first to note the importance of the diet in the production of fatty liver. He examined the bodies of four fowls which had died of phosphorus-poisoning, and found two had typical fatty livers and two had not. "Two fowls," he wrote, "were free from fat apparently owing to the breeding season. They also had no jaundice.

[1] Hence, in the normal heart, as in the liver, the greater part of the fat is in the form of lecithin (here about 70 per cent.). Rubow states that in muscle it is otherwise, only about 35 per cent. of the ethereal extract being composed of lecithin. In this case, apparently, the decrease in the amount of ethereal extract in starvation consists of fat.

[2] Rosenfeld has made the most exhaustive experiments with regard to this point, and given a very complete account of the question in the "Ergebniss der Physiologie."

The sections show conclusively that phosphorus-poisoning does not, under all circumstances, directly affect the liver. But it was not clear why the thin fowls did not show fatty livers like the plump ones. If we consider that the fatty liver in fowls is really due to the action of phosphorus, we can only properly assign to it a preparatory action on the liver, and suppose that it has the power of determining a large and abnormal influx of fat in the liver, thus laying it open to absorption and infiltration. Further cases and experiments will, of course, tell us whether the production of a fatty liver always depends on adequate nourishment, or whether phosphorus can produce it without this."

Lebedeff first propounded the "transference" hypothesis, which accounted for the fact that a very emaciated patient in Kussmaul's clinic did not exhibit a fatty liver. Von Starck described an "atrophic form" of phosphorus-poisoning. Finally, Rosenfeld carried out the following well-conceived experiments to determine the point, and was able to show that no "fatty liver" occurred in lean animals.

	Fat in Liver.		*Body Fat (Absolute).*	*Fat in Liver (Body Fat).*
	Dry Substance.	Absolute.		
	Per Cent.	Per Cent.	Per Cent.	Per Cent.
Starved fowls: normal ..	10·10	—	—	—
	9·43	0·451	7·370	6·0
	5·59	0·157	3·397	4·7
Starved fowls: phosphorus-poisoning	6·80	0·196	4·494	4·4
	12·00	0·346	3·520	9·8
	10·10	0·654	4·520	14·0

Rosenfeld's results were confirmed by Fibiger. In the absence of body-fat no fatty liver occurs; the fat does not arise in the liver, but is carried there from other parts—really from the adipose tissue between the viscera. Lebedeff had come to the same conclusion from an analysis of the liver fat and that from the subcutaneous tissues.[1] Other observers relied on the fact that the fat increased in the liver without an alteration in the total fat of the body, whilst Lebedeff's observation lent support to this view—that after feeding an animal with a foreign fat after phosphorus-poisoning, the same was found in the liver. This was confirmed by Rosenfeld. Leick and Winckler showed that the same theory applied to the heart. Woltke's experiments with estimates of the amount of saponification did not give such clear results, as the figures varied very much. Other experiments deal with feeding by means of iodine and Sudan fat (55 to 57). The first could be found invariably in the liver, but the results with the second were not constant (*cf.* also 58).

The last link in the chain is furnished by the fact that in phosphorus-poisoning there is a marked rise in the amount of fat in the blood. Moreover, in the liver, fat is found in the largest amounts where there is most blood (59). A progressive increase in the amount of the ethereal extract

[1] Kraus and Sommer found invariably a different amount of iodine in the two fats.

has been found in the lymph and in the blood ; in the latter it does not occur after ligature of the thoracic duct (48).

The next questions which arise are as to the form in which the transference of fat takes place, how it is effected, and for what reason.

With regard to the first question, the analytical results as to the heart and liver already quoted show that a somewhat complicated state of things exists, as in the liver there is an increase of fat and a decrease of lecithin, and in the heart an increase of both. It had been shown that the fat in the liver partly arises locally from lecithin (60), but subsequent investigations (130) disclosed objections to the methods employed ; the results are, in general, contrary to all the arguments previously adduced in favour of transference of fat, and an absolute increase in the total ethereal extract cannot be accounted for by a decrease in lecithin. Nothing certain is known as to the form in which the fat travels in the blood ; it is partly, perhaps, as lecithin ; at any rate, an ethereal extract of the blood of Rhine salmon was found rich in lecithin (61), " which was then decomposed with the formation of free fatty acids and soaps and disappeared " [Miescher]. There are no experiments *ad hoc*. Apparently, however, a part of the fat circulates as such. In nine poisoned frogs, contrary to normal, Taylor could extract no more fat by the digestion method than without it (62), so that he concluded than an exceptional process of decomposition was going on ; this important result ought to be confirmed by experiments on warm-blooded animals.

The transference of fat is not a specific result of phosphorus-poisoning ; it occurs after many other poisons and during starvation. In these cases, too, there is just the same excess of fat in certain organs—such as liver and heart—and there is no doubt that the process is a physiological one, and that the fat depots of the body are depleted in this way to meet the demand for fat in other parts of the body. The difference between the physiological and pathological process is that the latter does not cease when the demand of the organ for fat is satisfied ; hence the accumulation of fat in liver and heart under pathological conditions.[1] This may be completely or partly referred to the failure of the regulating mechanism, indirectly, at least, set in action by the demands of the organs. The nature of the mechanism can only be guessed ; there seem to be two possibilities : either the regulation is chemical and passes along the blood-stream, or is nervous. Meischer, in his remarkable researches on salmon, has shown that it is highly probable that the growth of the organs of generation, plus that of the spleen, causes them to attract a larger blood-supply, and produces secondarily an anæmia of those parts which require less blood. The relative decrease of oxygen in these parts then occasions a tissue change in which the fats take a large share. He then discusses the question as to whether in phosphorus-poisoning the fat transference is not due to a relative deficiency in oxygen in the places where fat is stored, possibly conditioned by some vasomotor changes. This hypothesis is strengthened by the fact that the fatty tissues are comparatively poor in bloodvessels, and so would be damaged by a

[1] Herxheimer and Walker Hall (*Med. Chron.*, 1904) propose the terms " fatty infiltration " and " degenerative fatty infiltration " for these two processes.

relatively slight decrease in oxygen. Whether this is due to an autodigestion of the thin membrane of the fat cell is not known. Even if Meischer's explanation of the physiological process is correct, we have no grounds for assuming a decreased circulation in the adipose tissue during phosphorus-poisoning. But there is another chemical theory which may account for the regulating mechanism. The composition of the blood may be changed [Lebedeff]. Some regulation for the liberation of fat might exist similar to the regulation for the conversion of glycogen by means of the sugar content of the blood. Possibly the sugar content itself may do it, as it has been clearly shown that many cases of abnormal accumulation of fat in the liver can be referred to a simultaneous increase in the carbohydrate supply. This, however, cannot apply to phosphorus-poisoning, as here the liver has lost the power of storing glycogen. As, then, this is not universally the case, no clear idea can be formed of the possible significance of the sugar content of the blood. Against any causal connection stands the fact that dogs in which the pancreas had been removed show a fatty liver, and at the same time a high sugar content in the blood. We must, however, remember that very probably sugar travels in the blood in a state of combination, and that when the power of combination is exceeded, free sugar appears in the circulation and is excreted. Now normally, also, a large portion of the fat in the blood is in combination. After a preliminary coagulation of the blood, a considerably larger ethereal extract was obtained than from uncoagulated blood. Whether there is any connection between sugar and fat combination is not known. Taylor found that in frogs poisoned by phosphorus all the body-fat was in a free state; this is contrary to the normal conditions, in which a greater part can only be extracted after digestion. We may speculate as to whether acidosis plays any part in the matter; in phosphorus-poisoning, as in other intoxications, and in diabetic coma,[1] there is always considerable decrease of alkalinity in the blood

As to a nervous regulatory mechanism, we may imagine that when a call occurs the hungry cells inform the depots via the nervous system, and that first glycogen, and then, when this is used up, fat is sent. Disturbances might arise owing to disturbances in the cell consumption, either due to special cell changes or due to the supply of fat in an unassimilable form. Perhaps the free absorption of chyle in phosphorus-poisoned animals may be connected with this (133). In both cases the cells remain hungry, the fat depots stimulated; thus occurs a prolonged emission of fat from the depots, and the deposit of the useless material in the localities where it should normally be utilized.

Protein Metabolism.

The nitrogenous excretion in man has been frequently investigated (70 to 80). Excluding those experiments in which the total amount of urine in the twenty-four hours was not measured, and those which were performed on persons *in extremis* (in which the final fall in nitrogen

[1] In this condition free fat is often found in the blood (lipæmia), though there is no absolute rise in the total amount [Schwartz (68)].

excretion is without special interest), certain researches against which no objection can be raised remain, the most complete being those of Badt. It is established by all these researches that the nitrogen excretion is considerably raised, and that the increase often begins on the second day, apparently as soon as all the glycogen has been used up for fuel (81 to 88). Falk only, who poisoned his dogs with enormous doses, so that they died within twenty-four hours, found the nitrogen excretion materially diminished (84). The same results are obtained in fed and fasting animals; sometimes, during the first day, there is a fall, or only a very slight rise, in the nitrogen excretion.

Clerc and Cook (151) found that the addition of inorganic phosphorus to phosphorus-free diet resulted in a negative phosphorus and nitrogen balance. Organic phosphorus increased both phosphorus and nitrogen retention when the food was poor in phosphorus, but no effect was obtained with a diet rich in phosphorus. Even after the addition of large amounts, no organic phosphorus was found in the urine.

Summary of the Experimental Results as to the Shares of Fat, Carbohydrate, and Protein in the Total Metabolism.

The total metabolism is decreased. That of protein is certainly increased, that of carbohydrate probably so; hence a corresponding marked fall in fat metabolism may be deduced, and has been shown to occur by numerous direct experiments.

Alkalinity of the Blood.

Many complete analyses show that the CO_2 content of rabbits' arterial blood is below normal during phosphorus-poisoning (66 to 68). Meyer has also found a very low proportion of CO_2 in a case in man. Titrimetric estimations also show diminished alkalinity (69). The cause lies in the entry of acids into the blood (*vide infra*)—such as lactic acid, and phosphoric and sulphuric acids—from the increased protein decomposition.

The Several Nitrogen Constituents of the Urine.

Earlier investigators, using what is now recognised as an inadequate method, found very little urea in the urine compared to the total nitrogen excreted. Newer experiments show the following results:

Badt's Table.

Case.	*Fifteen Grammes of Nitrogen excreted per Diem for Two Days.*				
	Total Nitrogen.	Urea Nitrogen.	Uric Acid Nitrogen.	NH_3 Nitrogen.	Residual Nitrogen.
1	100	69·9	3·14	7·77	19·19
2	100	41·7	0·01	25·80	32·49

MÜNZER'S TABLE.

Case.	*Fifteen Grammes of Nitrogen excreted per Diem for Two Days.*				
	Total Nitrogen.	Urea Nitrogen.	Uric Acid Nitrogen.	NH_3 Nitrogen.	Residual Nitrogen.
1	100	73·5	—	—	—
2	100	—	1·12	16·60	16·60
3	100	—	1·76	12·31	—
4	100	82·5	1·98	7·90	—
5	100	75·8	2·00	13·10	—
6	100	83·0	—	8·90	—
7	100	82·1	—	7·90	—
8	100	—	—	17·70	—
9	100	—	—	13·30	—
10	100	—	—	18·30	—
11	100	—	—	16·60	—
12	100	—	—	11·00	—
13	100	—	—	6·20 ($NaHCO_3$ *per os*)	—

In Laub's observations the urea nitrogen varied between 72 and 90 per cent. of the total. We may compare with these results the figures obtained from normal men :

Author.	*Total Nitrogen.*	*Urea Nitrogen.*	*Uric Acid Nitrogen.*	*NH_3 Nitrogen.*	*Extractives Nitrogen.*	*Amino-Acid Nitrogen.*
Von Noorden (90) ..	100	84–87	1–3	7–10	—	—
Hammarsten (91) ..	100	84–91	1–3	2–50	7–12	—
Camerer (92) ..	100	83–87	—	—	—	—
Pfaundler (93) ..	100	78·00	—	—	—	4·8
Kruger and Schmidt (94)	100	—	—	—	—	2·5–6·0

In dogs there is no marked decrease of urea nitrogen, and the ammonia is relatively increased.

Badt's figures, obtained by a method which gave too low a result, may be discarded, and the normal figures compared with Münzer's which are especially valuable as the experiments were carried out at all possible stages of phosphorus-poisoning. It will then be seen that in phosphorus-poisoning the organism excretes a smaller proportion of its urinary nitrogen in the form of urea than under normal conditions. The figures lie at the lower limit, and sink now and then below it, owing to the almost invariable increase in the ammonia excretion, which sometimes becomes excessive, and takes place at the expense of the urea. The urea and the ammonia nitrogen added together give the normal amount. The increased ammonia excretion is clearly a result of acidosis, as in one of Münzer's cases it was much decreased after the administration of sodium bicarbonate. The so-called residual nitrogen in Münzer's cases only amounted to about 8 per cent., about a normal average. This shows

that bodies not found at other times in the urine, even if they occur during phosphorus-poisoning, must do so in very small quantities. The presence of amino-acids is of special interest. Pfaundler obtained these figures :

Amino-Acids.

Normal dog, 2·26 per cent. ; after poisoning, 5·13 per cent.
„ „ 4·33 „ „ „ 7·0 „

The difference is distinct, though slight. Whether it is at the expense of the urea nitrogen, as seems to be the case from Pfaundler's analysis, cannot yet be definitely decided.

Components of the " Residual " Portion.

Oxyproteic Acid.—This substance, which occurs normally in the urine, is estimated along with the amino-acids (95). Careful estimations show that normally the amount varies between 2 to 3 per cent. of the total nitrogen. According to Pfaundler's figures, this would represent all the amino-acid nitrogen passed in health, and as it is said to be increased in phosphorus-poisoning, would also cover the increase in the residual nitrogen. This would be in agreement with the increase in neutral sulphur, though this can be otherwise explained (*vide infra*).

Cyanuric Acid.—This is said to be excreted in large quantities in dogs poisoned by phosphorus (131).

Peptone.—Gerhardt and others originally described the occurrence of peptone in the urine in cases of phosphorus-poisoning, and though these authors may really have been dealing with albumin, recent very reliable investigations show that in many such cases, when a negative result is obtained by boiling, or with the acetic acid and potassium ferrocyanide tests, bodies undoubtedly occur in the urine which give the biuret reaction (97 to 99, 100, 132). Particularly at the height of the illness the values were high, and then gradually sank. The nature of the body is uncertain, but it has nothing to do with the so-called " peptone-like " bodies discovered in dog's urine by Harnack (101), as none of these gave the biuret reaction.

Cystin.—Several authors have found a body from which sulphur is easily split off (102 to 104) ; it has been thought to resemble cystin. Careful researches have, however, failed to identify it, but it has been conclusively shown that phosphorus-poisoned dogs can elaborate cystin in the normal manner.

Amino-Acids—(*a*) *Glycocoll.*—The latest researches appear to show that this body regularly occurs in human urine, though it is not certain whether it is free or as a part of some more complex body. Hippuric acid, indeed, has been found in phosphorus-poisoned rabbits (105 to 108).

(*b*) *Alanin.*—This body has been shown to be probably present in the urine of cases of phosphorus-poisoning in man.

(*c*) *An optically active amino-acid*, not further identified, has been found in animals [Wohlgemuth].

(*d*) *Leucin.*—The presence of this body in the urine of moribund patients poisoned by phosphorus was shown to be probable by Fränkel and others (109, 125). It was identified by analysis by Blendermann (110) in the urine twenty-four hours before death. In the majority of carefully investigated cases hitherto it has not been found [Poore and others (111)], and it has never been identified in the urine of poisoned dogs.

Edgeworth, Walker Hall and Sheppard observed a case of phosphorus-poisoning in which a very marked jaundice and signs of severe intoxication cleared up, and the patient left the hospital apparently cured; large quantities of leucin were identified by the naphthalene-sulpho-chloride method. Arginin was sought for, but not found.

(*e*) *Tyrosin.*—Several observers have found this body to be present, and recognised it by analysis and microscopical and colour reactions. In many other cases it has been absent. It appears to occur more frequently in man than leucin, but by no means regularly; it has only been once found in dogs, and that in a doubtful case (112).

(*f*) *Arginin* has been found in the urine of rabbits and man after poisonous doses of phosphorus (152).

Significance of the Appearance of Amino-Acids.

Though little can be said as to the causes of the increase of oxyproteic acid, or the occurrence of peptone and cystin-like bodies, some more detailed consideration must be given to the problem of the amino-acids, and the meaning of their occurrence. Their presence, especially that of leucin and tyrosin—for the others have but recently been isolated—has from the first excited considerable interest, as they have very generally been regarded as the intermediate products of normal metabolism, the further breaking down of which has been hindered by the peculiar conditions of phosphorus-poisoning. This assumption is not, however, *a priori* justified. The appearance of the amino-acids in phosphorus-poisoning only shows that the organism *can* construct them, not that it *does* so under normal conditions. Just as the formation of comparatively simple organic bodies may be influenced in various directions by the introduction of certain groups, so we are able to influence the direction of protoplasmic katabolism by various means—*e.g.*, by introduction of certain atom groups. Thus antibodies are produced, and thus the glycocoll combination from benzoic acid. We have no right, however, to assume that normally just as much glycocoll is split off as when benzoic acid is administered; or, similarly, that amino-acids are normally formed owing to their occurrence in the urine in phosphorus-poisoning. Possibly the phosphorus, like the benzoic acid, may, by setting up peculiar conditions, influence the protoplasm and induce exceptional processes. We must therefore inquire whether there is any reason for thinking that amino-acids occur during normal metabolism. Our ideas as to their significance in phosphorus-poisoning can only be rightly framed on the results of such investigations.

The digestion of protein in the intestinal canal undoubtedly gives rise to these bodies, as they have been found there. Glycocoll is regularly formed as an intermediate product after the administration of benzoic and salicylic acids and other bodies, and is found combined with them in the urine. Whether it can occur apart from these combinations is unknown. Leucin is not found under normal conditions in the blood or organs, even after large doses are given by the mouth (108, 116), and an increase in the urinary amino-acids has only been noted after their intravenous injection in rabbits (117). Tyrosin itself does not easily pass into the urine; in rabbits, the ingestion of large quantities gives rise to tyrosin-hydrantoin in the urine, and intravenous injections produce an increase in amino-acids (*vide infra*). This negative result does not disprove their occurrence normally, as the organism can oxidize large amounts of leucin.

We know more of the normal formation of tyrosin, which is another product of the intestinal digestion of protein. It is also certain that it is an intermediate product of metabolism. In starved animals whose intestines were quite empty, and in aseptically-fed guinea-pigs, bodies are constantly found in the urine which are derived from tyrosin, and are increased when large quantities of that substance are given by the mouth. They are the de-amidization and oxidation products of tyrosin, the so-called aromatic oxyacids, para-oxy-phenyl-propionic acid, and para-oxy-phenyl-acetic acid; para-oxy-phenyl-lactic acid does not occur normally, but only after tyrosin administration. The conditions found in alkaptonuria all point in the same direction.

To sum up: Under normal circumstances the occurrence of glycocoll and leucin is not proved, but that of tyrosin is highly probable.

To answer the question as to how the appearance of these bodies in phosphorus-poisoning is to be explained, we must first determine whether they represent a specific disturbance of metabolism. This is not the case. In the first place, phosphorus-poisoning is not invariably accompanied by the presence of amino-acids; they are absent in many cases, so that there is no actual qualitative disturbance. In the next place, recent accurate methods have enabled us to recognise the presence of amino-acids in the urine in a large number of conditions—for instance, in the course of severe jaundice, narcosis, and diabetes (96, 106, 134). In all probability the number of instances will be greatly increased in the next few years.

Of especial importance, however, as facilitating an explanation of the etiology, are observations on the occurrence of amino-acids in cases in which the oxygen consumption has been experimentally decreased. This happens either through diminution of the supply of oxygen to the tissues—residence at high altitudes (123), autolysis—or through decrease in their oxidative power—prussic acid poisoning (124). Most probably the decreased consumption of oxygen causes a further remarkable condition—namely, decreased alkalinity. Autolysis does not occur in neutral, or alkaline, media; at any rate, not to the extent with which we are dealing here—the hydrolysis of protein as far as the production of amino-acids (135 to 137). It would be very significant if it could be

shown that amino-acids were present in the urine of animals under varied conditions of acidosis, deprivation of oxygen, or prussic acid poisoning.

The idea that in phosphorus-poisoning a condition of anaerobiosis exists is no new one. Experimental work was first carried out on the subject by Jacobi (113), who considered that there was considerable *ante-mortem* autolysis in this condition, on account of his observation that in a case in a dog a larger proportion than usual of the total nitrogen in the liver could be precipitated with magnesia, and, further, that if the phosphorus liver were allowed to stand, more nitrogen could be obtained by magnesia, and, finally, a rapid disintegration of the tissues occurred. The latter phenomenon has probably no connection with changes in the protein bodies, as the coagulable nitrogen did not decrease any more rapidly than in a normal liver. Possibly it was due to a solution of the fat of the liver in the toluol. It has not been determined whether there is a greater proportion of amide nitrogen than non-amide in the phosphorus liver. *A priori*, a more marked autolysis in the phosphorus liver is not surprising, as it is favoured by the acid reaction.

An entirely different point of view is taken up by Welsch (5). He endeavoured to ascertain whether the occurrence of diamino-acids arises from their increased formation to such an extent that the normal oxidizing capacity of the organism is not equal to their complete decomposition, as when large amounts are given by the mouth ; or whether it is due to a decreased power of oxidation or synthesis, the extent of the production remaining normal ; or, finally, whether a combination of both factors exists. If, normally, amino-acids are usually formed as intermediate products—which seems very probably the case with tyrosin—it might, *a priori*, be assumed that they would occur to a greater extent in phosphorus-poisoning, as the protein metabolism is increased, provided that the latter proceeds in the usual manner. If, however, this is not so—as, for instance, in autolysis of the organs—still greater amounts of amino-acids will occur. We may infer from this increased metabolism that the power of the normal organism to decompose excessive amounts of amino-acids is absent, and are thus compelled to conclude that, besides increased formation, there is also decreased power of oxidation. This is also the conclusion arrived at with more certainty by Baumann and his pupils (110, 120, 122, 126).

1. Observations on Man.

Condition.	*Urinary Excretion of—*		
	Phenol.	Oxyacids.	Tyrosin.
Normal	Traces.	Traces.	Nil.
5–10 grammes tyrosin ..	Increased.	Traces.	Nil.
Phosphorus-poisoning ..	Increased.	Much increased.	Nil or traces.

2. Observations on Dogs.

Condition.	Urinary Excretion of—		
	Phenol.	Oxyacids.	Tyrosin.
Normal	Traces.	Traces.	Nil.
Tyrosin, 5 grammes	Traces.	Traces or increase.	Nil or traces.
Tyrosin, 10 grammes ..	Traces.	Considerable increase.	Traces.
Phosphorus-poisoning ..	Traces.	Increased.	Nil.
Phosphorus-poisoning + 10 grammes tyrosin	Traces.	Considerable increase.	Nil or traces.

From this table it is clearly seen that, even in phosphorus-poisoning, the power of de-amidization[1] is only very seldom insufficient, and is fairly adequate when the organism has to deal with even large quantities of amino-acids.

On the other hand, in phosphorus-poisoning the oxyacids are not only increased in dogs, which normally excrete more oxyacids if fed with tyrosin, but also in men, who only excrete more phenol. This points to an abnormal metabolism, as does the appearance of oxymandelic acid—a tyrosin nucleus which up to the present, at any rate, has never been found in health (126, 127).

If we might draw conclusions as to the other amino-acids from the fate of tyrosin, we should consider that in phosphorus-poisoning probably there is an increased production of amino-acids and a decreased power of decomposing them. The metabolic disturbances primarily affect oxidation (failure to convert oxyacids into phenol) and only under special circumstances the de-amidization[2] (just before death).

Non-nitrogenous Bodies of the Aliphatic Series.

Sarcolactic acid has been found in increased quantities in the organs and urine, both in man and animals, during phosphorus-poisoning, but frequently it is absent, and in cats less than the usual amount has been found in muscle [Mandel and Lusk, and others (150)]. In phlorizin glycosuria the sarcolactic acid disappears from the blood and urine of phosphorus-poisoned animals.

Acetone.—In man this has been found immediately after the poisoning, and apparently independently of starvation. Schwartz concluded that it was not connected with malnutrition, as it increased in spite of the administration of carbohydrates (149).

[1] This is the form of disturbance when unchanged tyrosin appears in the urine.

[2] It has been shown that tyrosin only appears in the urine shortly before death, and that amino-acids cannot be found in the organs at the height of the poisoning (114). Probably the synthesis of amino-acids into higher compounds is disturbed; it has been shown that there is less hippuric acid formed (138); whereas the phenol-sulphonic acid remains unchanged (139).

The Inorganic Constituents of the Urine.

1. *Chlorides.*—Observations on man and animals unite in showing that at the beginning of the poisoning the chlorides rapidly fall, then gradually rise till they exceed the normal amount. Until experimental results showing the balance between output and intake are available, it is impossible to say whether this is due solely to the commencing starvation, or whether it is produced by various factors.

2. *Phosphates.*—In observations on man during the first twenty-four hours the phosphorus excretion compared to the nitrogen remained about normal; there was then a rapid rise for a few days, and then a fall to subnormal; finally, a rise to normal. No balance-sheet could be drawn up owing to ignorance of the intake. Münzer regarded the original rise (which his colleagues attributed to the oxidation of some of the phosphorus to phosphoric acid) as indicating the destruction of lecithin in the liver; lecithin has been shown to be decreased (*vide supra*). The subsequent fall, he thought, showed its renewed formation. Other observers found that the phosphorus excretion parallel with that of nitrogen (*cf.* also 151).

3. *Sulphates.*—No special increase has been recognised by Kast and Münzer. Welsch, however, found a distinct but transient increase in sulphur excretion which did not, as in other poisoning cases, vary exactly as did the nitrogen. Figures have already been quoted for the unoxidized sulphur. Estimations of the ethereal sulphates yielded negative results.

The Theory of Phosphorus-Poisoning.

Having now considered the symptomatology of phosphorus-poisoning, we must inquire whether we are in a position to explain its action. It is very doubtful whether phosphorus acts as an element, or in a reduced or oxidized form (140). Ever since Bauer's experiments the symptoms have been compared with those of oxygen deficiency in tabular form thus:

	Deficiency of Oxygen.	Phosphorus-Poisoning.
1.	*Gaseous metabolism:*	
	O_2 intake decreased.	O_2 intake decreased.
	CO_2 output at first increased or unchanged, finally decreased.	CO_2 output at first not investigated, generally decreased.
2.	*Fat metabolism:*	
	Apparently decreased.	Apparently decreased.
3.	*Glycogen content:*	
	Diminished.	Diminished.
4.	*Sugar in blood:*	
	Often raised with glycosuria.	Not raised; glycosuria infrequent.
5.	*Blood gases.*	
	O_2 decreased.	Not decreased.
	CO_2 decreased.	Decreased.
5a.	*Alkalinity of blood:*	
	Decreased.	Decreased.

Deficiency of Oxygen.	Phosphorus-Poisoning.
6. *Fat transference and infiltration :*	
Not investigated.	Present.
7. *Protein Metabolism :*	
Increased.	Increased.
8. *End-products—*	
(*a*) Nitrogenous :	
Amino-acids sometimes present.	Sometimes present.
Oxyproteic acid—not investigated.	Increased.
Peptone—not investigated.	Sometimes present.
(*b*) Non-nitrogenous :	
Lactic acid present.	Present.
Normal oxyacids—not investigated.	Increased.
Oxymandelic acid—not investigated.	Sometimes present.
9. *Hippuric acid synthesis :*	
Diminished.	Diminished.
10. *Neutral sulphur :*	
Increased.	Increased.

We cannot, of course, expect the two processes to be identical, as they are not produced by identical agencies. Phosphorus-poisoning is usually a chronic process, whereas deprivation of oxygen under experimental conditions is usually acute. Hence, too, experiments on oxygen deprivation show very various results, according to the degree of acuteness, and certain points on both sides are as yet very imperfectly investigated. The table, however, shows many analogies, chiefly as regards (2) fat metabolism, (3) condition of glycogen, (5) CO_2 in blood, (5*a*) alkalinity of blood, (7) protein metabolism, (8, *a*) amino-acids, (8, *b*) lactic acid, (9) restricted synthesis of hippuric acid, (10) increase of neutral sulphur. Inadequate or unsuccessful experiments render it impossible at present to compare the behaviour of the gaseous metabolism and the occurrence of peptone, oxyproteic acid, oxyacids—especially oxymandelic acid—fat transference, and infiltration.

The behaviour of the sugar in the blood (and urine) is quite different under the two conditions, being increased in oxygen deficiency and usually absent in phosphorus-poisoning. Anyhow, the more careful experiments fail to show under what conditions glycosuria occurs in phosphorus-poisoning ; whereas it is quite certain that in acute deprivation of oyxgen—though usually not in chronic—a marked breaking down of glycogen occurs, and is apparently vasomotor in origin.

The very general agreement in the symptomatology of the two conditions suggests that actually a deficiency of oxygen may occur in phosphorus-poisoning. This might be caused by a disturbance of the respiration or circulation, or both. No disturbance of respiration has ever been observed, but as to the circulation, Miescher, as we have seen, regarded as an important factor the disturbance which occurs very early in the acute cases, and towards the end in the chronic ones. Meyer excluded the circulatory disturbances as a cause of the fatty liver in rabbits because

the blood-pressure falls markedly ; and, on the other hand, other poisons, like iron, platinum, and emetin—which equally reduce the blood-pressure —do not produce fatty infiltration. We do not consider that the circulatory disturbance is the cause of most of the symptoms, but think it probable that it has some connection with the appearance of leucin and tyrosin in the liver and urine, as these substances are not found when the symptoms are at their height, but only just before death.

The blood-supply may suffer owing to changes in the blood—either a decrease in the erythrocytes, or a change in the hæmoglobin. In certain classes of animals, as a matter of fact—*e.g.*, birds—a considerable fall in erythrocytes occurs (148). In mammals only a slight diminution, if any, takes place ; generally there is a relative increase in erythrocytes and hæmoglobin owing to increased density of the blood (115). The decrease has no causal relation to the symptoms. Meyer showed that a rabbit which, in the course of a fortnight, had lost twice its original amount of blood showed no decrease in the CO_2, though the O_2 in the blood was much diminished. The latter is not decreased in phosphorus-poisoning.

Although Meyer could find no change of any other kind in the blood which would prevent the oxygen being given up to the tissues—as when methæmoglobin is formed—Araki states that the phosphorus prevents the blood from parting so rapidly with its oxygen.

We may, therefore, on the experimental evidence, exclude decreased oxygen supply to the tissues as a cause of the symptom-complex in phosphorus intoxication.

As, however, there are undoubted signs of diminished energy in the oxidizing processes, we must consider whether phosphorus may not act like prussic acid, only much more slowly, and directly inhibit the oxidative capacity of the cells. In this case we should expect the same signs of partially anaerobic processes as in deprivation of oxygen. We must remember that possibly phosphorus has some selective affinity for the constituents of certain organs, and that the disturbances might, in consequence, be limited to these. To deal with the latter point first, there are many indications of especially severe disturbances in the liver, whence it frequently happens that in spontaneous cases of poisoning in animals these only are noted. Very probably, however, there are also severe changes in other organs, as is indicated by the presence of protein hydrolysis (amino-acids) in the kidneys, muscles, and heart.

On the other hand, the temporary character of the functional derangement in such organs as the brain and kidneys is against this view.

The changes in the liver are the only ones which have been completely studied. Besides the increase in fat and decrease in lecithin, they include diminution in the total nitrogen, which is absolute and not merely relative to the increase in fat, and an absolute diminution in the protein bases, as shown by the following table [Kossel and Wakeman (142)]:

Condition.	*Nitrogen.*	*Total Nitrogen in—*		
	Dry Substance.	Arginin.	Histidin.	Lysin.
	Per Cent.	Per Cent.	Per Cent.	Per Cent.
Normal	11·54	8·98	2·0	4·87
	11·28	10·25	2·4	5·50
	12·48	8·72	2·4	3·90
Phosphorus-poisoning ..	7·34	5·05	1·8	3·80
	7·90	4·14	1·2	2·70

The liver does not appear to lose either sulphur or phosphorus [Wohlgemuth (143)].

Condition.	*Dry Substance in—*		
	Nitrogen.	Phosphorus.	Sulphur.
	Per Cent.	Per Cent.	Per Cent.
Normal	11·42	1·82	0·78
Phosphorus-poisoning ..	7·26	1·77	0·81

It would be interesting to determine whether similar changes occur in the liver in cases of deprivation of oxygen, especially when produced by poisons like prussic acid, which directly diminish the oxidative power of the cells. As a matter of fact, the phenomena are best correlated by supposing that the symptoms of phosphorus-poisoning are due to the power of the poison to diminish the oxidative capacity of the cells, especially in certain organs. It thus resembles a chronic prussic acid poisoning, and it is this chronic character which prevents the oxygen content of the venous blood from giving so decisive a result, though, but for the fact that it gives an abnormally high figure, it furnishes considerable support to the opinion we have advanced.

This also explains why fermentative processes are not diminished (144); benzoyl oxidation alone is restricted, though possibly this is the result of some indirect disturbance of oxidation—namely, diminished fat metabolism (145).

LITERATURE.

1. Bauer: Der Stoffumsatz bei der Phosphorvergiftung. Z. B. **7.** 63. 1871.
2. Monaco: Der respirat. Gaswechsel bei Phosphorvergiftung. Bu. R. **79.** Nr. 2. 1893.
3. Scheider: Einige exper. Beitr. zur Kenntnis der Phosphorvergiftung. Diss. Würzb., 1895.
4. Athanasiu: Die Erzeugung von Fett im tier. Körper unter dem Einfluss von Phosphor. Ar. P. M. **74.** 511. 1899.
5. Welsch: Sur la pathogénie des lésions anat. dans l'intoxication phosphorée aigue. Ar. i. P. **14.** 181. 1905.
6. Leo: Fettbild. und Fett-transport bei Phosphorvergiftung. Z. p. C. **9.** 469. 1885.

7. Schmitt: Ueber den Fettgehalt der Tiere nach Phosphorvergiftung. Diss. Bonn, 1885.

8. Bergeat: Fettbild. bei Phosphorvergiftung. Mü. m. W. **1888.** P. 66.

9. Kraus u. Sommer: Ueber Fettwanderung bei Phosphorintoxikation. Beitr. phys. Ch. **2.** 87. 1902.

10. Polimanti: U. die Bild. von Fett im Organismus nach Phosphorvergiftung. Ar. P. M. **71.** 349. 1898.

11. Pflüger: Physiol. der Fettbild., des Glykogens und der Phosphorvergiftung. Ar. P. M. **71.** 318. 1898.

12. Taylor: The Origin of Fat from Protein in the So-called Fatty Metamorphosis of Phosphorus-Poisoning. J. E. M. **4.** 399. 1899.

13. Magnus: Ueber die Entsteh. der Hautödeme bei exper. hydrämischer Plethora. E. A. **42.** 250. 1899.

14. Saikowski: Ueber die Fettmetamorph. der Organe nach innerem Gebrauche von Arsen-, Antimon- und Phosphorpräparaten. Ar. p. A. **34.** 73. 1865.

15. Rosenbaum: Über den Kohlenhydratbestand des tier. Organismus nach Vergiftung mit Arsenik, Phosphor, Strychnin, Morphium, Chloroform. Diss. Dorpat, 1879.

16. Luchsinger: Beitr. zur Physiol. und Pathol. des Glykogens. Diss. Zürich, 1875.

17. Neubauer: Private communication.

18. Kaufholz: Ueber das Verhalt. des Leberglykogens und Blutzuckers nach Phosphorvergiftung. Diss. Würzb., 1898.

19. Mohr: Ueber das Verhalt. der Kohlenhydr. im Körper phosphorvergifteter Tiere. Z. e. P. **1905.** 1.

20. Zuntz u. Vogelius: Ueber die Neubild. von Kohlenhydraten im hungernden Organismus. D. A. **1893.** 378.

21. Frentzel: Ueber Glykogenbild. im Tierkörper nach Fütterung mit Holzzucker. Ar. P. M. **56.** 273. 1894.

22. Nebelthau: Zur Glykogenbild. in der Leber. Z. B. **28.** 138. 1901.

23. Hirsch u. Rolly: Zur Frage der Entstehung von Glykogen aus Körpereiweiss. D. Ar. M. **78.** 380. 1903.

24. Rolly: Ueber die Neubild. von Glykogen bei glykogenfreien und auf Karenz gesetzten Kaninchen. D. Ar. M. **88.** 107. 1905.

25. Rosenfeld: Fettbildung. II. Er. Ph. II. **1.** 50. 1903.

26. Bollinger: Ein Fall von Phosphorvergiftung. D. Ar. M. **6.** 94. 1860.

27. Huber: Klin.-toxikolog. Mitteilungen. Z. M. **14.** 479.

28. Frerichs: Ueber den Diabetes. 1884.

29. Reichel: Ein Fall von akuter Phosphorvergiftung. W. k. W. **7.** 153. 1894.

30. Laub: Ueber Glykosurie bei akuter Phosphorvergiftung. W. k. W. **10.** 27. 1898.

31. von Jaksch: K. i. M. **16.** 117. 1898.

32. Walko: Ueber spontane und aliment. Glykosurie und über Azetonurie bei akuter Phosphorvergiftung. Z. H. **22.** 8. 1901.

33. Araki: Beitr. zur Kenntnis der Einwirk. von Phosphor und von arseniger Säure auf den tier. Organismus. Z. p. C. **17.** 311. 1893.

34. Embden u. Salomon: Fütterungsvers. am pankreaslosen Hund. Be. P. P. **6.** 63. 1904.

35. Rose: Der Blutzuckergeh. des Kaninchens. E. A. **50.** 15. 1903.

36. May: Der Stoffwechsel im Fieber. Z. B. **30.** 1. 1894.

37. Baldi: A. F. **2.** 490. 1894.

38. Lusk, Ray, MacDermott: On Metabolism during a Combination of Phosphorus-Poisoning and Phloridzin Diabetes. A. J. P. **3.** 139. 1899.

39. Münzer: Der Stoffw. des Menschen bei akuter Phosphorvergiftung. D. Ar. M. **52.** 199, 417. 1894.

40. von Starck: Beitr. zur Pathol. der Phosphorvergiftung. D. Ar. M. **35.** 481. 1885.

41. Heffter: Das Lezithin der Leber und sein Verhalten bei der Phosphorvergiftung. E. A. **28.** 97. 1890.

42. Carbone: Sur l'origine de la graisse dans les processus dégénératifs. Ar. i. B. **26.** 279. 1896.

43. Rubow: Ueber den Lezithingeh. des Herzens und der Nieren unter norm.

Verhält., im Hungerzustand und bei der fettigen Degeneration. E. A. **52.** 173. 1905.

44. Stolnikow: Vorgänge in den Leberzellen, insbes. bei Phosphorvergiftung. D. A. **1887.** Suppl. 1.

45. Krehl: Ueber die fettige Degen. des Herzens. D. Ar. M. **51.** 416. 1894.

46. Leick u. Winkler: De Herkunft des Fettes bei Fettmetamorph. des Herzfleisches. E. A. **48.** 163. 1902.

47. Lusena: Ueber den Lezithingeh. der Leber, der Nieren und des Herzens bei der exper. Fettdegeneration. S. **57.** 29. 1903. Ma. **33.** 90. 1903.

48. Bonanni: Ueber die Herkunft des Fettes bei Pulegonvergiftung. A. F. s. **2.** 97. 1903.

49. Leisering: Phosphorvergift. bei Hühnern. Ar. p. A. **30.** 478. 1864.

50. Lebedeff: Woraus bildet sich das Fett in Fällen der akuten Phosphorvergiftung? Ar. P. M. **31.** 11. 1883.

51. Fibiger: Ueber die Entwickel. der fettigen Degeneration. N. m. A. **1901.** 2.

52. Daddi: Sull' origine dell grasso nell avvelenamento per fosforo. S. **51.** 3. 1898.

53. Méhu: Analyses de liquides pleurétiques chargés de matières grasses. Ar. g. m. **2.** 5. 1886.

54. Woltke: Ueber die Veränderungen des Fettes infolge der Phosphorvergiftung. Diss. (Moscow.) Ma. **1901.** 77.

55. Schwalbe: Über Fettwanderung bei Phosphorvergift. mit Hilfe des Jodipins. Mü. m. W. **1903.** 2029.

56. Cavazza: Contrib. alla dottrina della degenerazione grassa. P. **9.** 16. 1. 1903.

57. Wells: Über den Transport von jodiertem Fett bei Phosphorvergiftung. Z. p. C. **45.** 412. 1905.

58. Lindemann: Ueber das Fett des norm. und des fettig entarteten Herzmuskels. Z. B. **38.** 405. 1899.

59. Cornil et Brault: Recher. histol. relatives à l'état du foie, du rein et du poumon dans l'empois. par le phosphore et par l'arsénie. J. A. P. **28.** 1. 1882.

60. Waldvogel: Die fettige Degeneration. C. S. **4.** 405. 1903.—Phosphorvergift. und Autolyse. D. Ar. M. **82.** 437. 1903.

61. Miescher: Die histochem. und physiol. Arbeiten. 1897.

62. Taylor: On Fatty Degeneration. J. M. R. **9.** 59. 1903.

63. Perls: Zur Unterscheid. zwischen Fettinfiltration und fettiger Degeneration. C. m. W. **1873.** 802.

64. von Hösslin: Ueber den Fett- und Wassergeh. der Organe bei versch. patholog. Zuständen. D. Ar. M. **33.** 601. 1883.

65. Schwarz: Über Diabetes. D. Ar. M. **76.** 233. 1903.

66. Meyer: Ueber die Wirk. des Phosphors auf den tier. Organismus. E. A. **14.** 313. 1881.

67. Loewy u. Münzer: Beitr. zur Lehre von der exper. Säurevergiftung. D. A. **1901.** 81, 174.

68. Kraus: Ueber die Alkales. des Blutes bei Krankheiten. Z. H. **10.** 155. 1889.

69. von Jacksch: Beitr. zur Kenntnis der akuten P-Vergiftung des Menschen. D. m. W. **19.** 10. 1893.

70. Schultzen u. Reiss: Ueber akute Phosphorvergift. und akute gelbe Leberatrophie. Ch. An. **15.** 1. 1869.

71. Riess: Phosphorvergiftung. Real-Enzykl. d. ges. Heilk. **19.** 63. 1898.

72. Fränkel: Ein Beitr. zur Lehre von der akuten Phosphorvergiftung. B. k. W. **1878.** 265.

73. Poore: On Two Cases of Phosphorus-Poisoning. L. **1888.** 1055.

74. Huber: l. c. (27).

75. Badt: Versuche und klin. Beitr. zur Lehre vom Stoffwechsel bei Phosphorvergiftung. Diss. Berlin, 1891.

76. Münzer: l. c. (39).

77. Laub: l. c. (30).

78. Rossi: Der Stickstoffumsatz bei akuter Phosphorvergiftung. P. **5.** Nr. 7. **1898.**

79. Reichel: Ein Fall von akuter Phosphorvergiftung. W. k. W. **7.** 153. 1894.
80. G. Rem Picci: Richerske dut ricambio materiale nel uomo nel avelenamento acuto per fosforo. Boll. cl. acc. d. Roma. **28.** 5. 1901.
81. J. Bauer: l. c. Ueber die Eiweisszersetz. bei Phosphorvergiftung. Z. B. **14.** 527. 1878.
82. Cazeneuve: De l'infl. du phosphore sur l'excrét. urinaire. G. m. P. **1879.** 667.
83. Storch: Den acute Phosphorvergift. i toxikologisk, klinisk og forensisk Hensoede. 1865. E. A. **7.** 570. 1877.
84. Engelien: Ueber das Verhalt. der Ammoniakaussch. bei Phosphorvergiftung. Diss. Königsb., 1887.
85. Thibaut: Des variations de l'urée dans l'empoisonn. par le phosphore. C. r. S. B. **90.** 1173. 1880.
86. Kast: Ueber Beziehungen der Chloraussch. zum Gesamtstoffw. Z. p. C. **12.** 267. 1888.
87. Monaco: Effetti dell' avelenamento lento per fosforo sul ricambio materiale. Arch. di pharm. e terap. **4.** 373. 1896.
88. Fränkel u. Röhmann: Phosphorvergift. bei Hühnern. Z. p. C. **4.** 439. 1880.
89. Falck: Der inanitielle Stoffw. und seine Bedeut. für Pharm. und Toxikologie. E. A. **7.** 570. 1877.
90. von Noorden: Stoffwechsels. 1893. P. 63.
91. Hammarsten: Physiological Chemistry. Trans. by Mandel. New York. 1904.
92. Camerer: Gesamtstickstoff, Harnstoff, Harnsäure und Xanthinkörper im menschl. Urin. Z. B. **28.** 72. 1891.
93. Pfaundler: Ueber ein Verfahren zur Bestim. des Amidosäurestickstoffs im Harn. Z. p. C. **30.** 75. 1900.
94. Krüger u. Schmid: Bestim. des Aminosäuren-N im Harn. Z. p. C. **31.** 556. 1901.
95. Gottlieb u. Bondzynski: Ueber die Oxyproteinsäure. C. m. W. **1897.** Nr. 33.
96. Abderhalden: Abbau und Aufbau des Eiweisses im tier. Organismus. Z. p. C. **44.** 50. 1905.
97. Maixner: Ueber Peptonurie. P. V. **143.** 75. 1879.
98. von Jaksch: Ueber die klin. Bedeut. der Peptonurie. Z. M. **6.** 413. 1882.
99. Robitschek: Beitr. zur Frage der Peptonurie bei der akuten Phosphorvergiftung. D. m. W. **1893.** Nr. 24.
100. Münzer: l. c. (39).
101. Harnack: Ueber den sog. peptonartigen Körper im Hundeharn bei Phosphorvergiftung. B. k. W. **1893.** Nr. 47.
102. Goldmann u. Baumann: Zur Kenntnis der schwefelhaltigen Verbindungen des Harns. Z. p. C. **12.** 254. 1888.
103. Petry: Ueber die Aussch. von leicht abspaltbarem Schwefel durch den Harn. Z. p. C. **30.** 45. 1900.
104. Blum: Ueber das Schicksal des Cystins im Tierkörper. Be. P. P. **5.** 1. 1904.
105. Embden u. Reese: Ueber die Gewinnung von Aminosäuren aus norm. Harn. Be. P. P. **7.** 411. 1905.
106. Samuely: Zur Frage der Aminosäuren im Pathologischer Harn. Z. p. C. **47.** 376. 1906. Walker Hall: B. J. 1906.
107. Wohlgemuth: Zur Kenntnis des Phosphorharns. Z. p. C. **44.** 74. 1904.
108. Abderhalden u. Bergell: Ueber das Auftreten von Monoaminosäuren im Harn von Kaninchen nach Phosphorvergift. Z. p. C. **39.** 464. 1903.
109. Wyss: Ueber das Vorkom. von Leuzin und Tyrosin bei Phosphorvergift. Z. H. **3.** 321. 1864.
110. Blendermann: Beitr. zur Kenntnis der Bild. und Zersetz. des Tyrosins im Organismus. Z. p. C. **6.** 234. 1882.
111. Hoppe-Seyler: Phys. Chemie. **1881.** P. 989.
112. Lusk: l. c. (38).

113. Jacoby: Ueber die Bezieh. der Leber und Blutveränderungen bei Phosphorvergift. zur Autolyse. Z. p. C. **30.** 135. 1900.
114. Hirschler: Beitr. zur Analyse der N-halt. Substanzen des Tierkörpers. Z. p. C. **11.** 24. 1886.
115. H. Welsch: Modifications du sang dans l'intoxication phosphorée. Ar. i. P. **14.** 197. 1905.
116. Loewy u. Neuberg: Ueber Cystinurie. Z. p. C. **44.** 338. 1904.
117. Stolte: Schicksal der Monoaminosäuren nach Einführung in die Blutbahn. Be. P. P. **5.** 15. 1904.
118. Baumann: Die aromat. Verbind. im Harn und die Darmfäulnis. Z. p. C. **10.** 127. 1886.
119. Nuttall u. Tierfelder: Tierisches Leben ohne Bakterien im Verdauungskanal. Z. p. C. **21.** 109. 1895. **22.** 62. 1896.
120. Brieger: Ueber Phenolaussch. bei Krankh. und nach Tyrosingebrauch. Z. p. C. **2.** 241. 1878.
121. Küssner: Zur Lehre von den Vorstufen des Harnstoffs. Diss. Königsb., 1874.
122. Schotten: Das Verhalt. des Tyrosins im Tierkörper. Z. p. C. **7.** 23. 1882.
123. Loewy: Ueber Störungen des Eiweiss-stoffw. beim Höhenaufenthalt. D. m. W. **1905.** Nr. 48.
124. Loewy: Über exper. Störungen des Eiweissabbaues. C. P. **19.** 23. 1906.
125. Ossikowski: Ueber Phosphorvergift. und akute gelbe Leberatrophie. W. m. P. **1872.** 5.
126. E. Baumann: Ueber den Nachweis und die Darstell. von Phenolen und Oxysäuren aus dem Harn. Z. p. C. **6.** 183. 1882.
127. von Ackeren: Quoted by Badt (75), p. 44.
128. Morishima: Ueber das Vorkom. der Milchsäure im tier. Organismus mit Berücksichtigung der Arsenvergiftung. E. A. **43.** 217. 1899.
129. Lusk and Mandel: Lactic Acid in Intermediary Metabolism. A. J. P. **16.** 129. 1906.
130. Meinertz: Zur Chemie der Phosphorleber. Z. p. C. **44.** 371. 1905.
131. Mendel u. Schneider: Ueber Ausscheidung von Kynurensäure. A. J. P. **5.** 427. 1901.
132. Fischel: Ueber puerperale Peptonurie. Ar. Gy. **24.** 3. 1884.
133. Sotnitschewsky: Ueber Phosphorvergiftung. Z. p. C. **3.** 391. 1879.
134. Abderhalden u. Schittenhelm: Aussch. von Tyrosin und Leuzin in einem Fall von Zystinurie. Z. p. C. **45.** 468. 1905.
135. Hedin and Rowland: On the Proteolytic Enzymes of the Spleen. J. P. 1903. **30.** 155.
136. Wiener: Ueber den Einfluss der Reaktion auf autolyt. Vorgänge. C. P. **19.** 349. 1905.
137. Bär u. Löb: Ueber die Beding. der autolyt. Eiweiss-spaltung in der Leber. E. A. **51.** 1. 1904.
138. Hauser: Beitr. zur Kenntnis der Phosphorwirkung. E. A. **36.** 165. 1895.
139. Nencki u. Sieber: Ueber eine neue Methode, die physiol. Oxydation zu messen und über den Einfl. der Gifte und Krankh. auf dieselbe. Ar. P. M. **31.** 319. 1883.
140. Kunkel: Handb. der Toxikologie. **1.** 1899.
141. Taussig: Ueber Blutbefunde bei akuter Phosphorvergiftung. E. A. **30.** 161. 1892.
142. Wakeman: Ueber die chem. Veränderungen der Leber bei der Phosphorvergift. Z. p. C. **44.** 335. 1904.
143. Wohlgemuth: Zur Chemie der Phosphorleber. Zt. Bioch. **1.** 161. 1906.
144. Kluge: Über die Wirk. des Phosphors nebst Bemerkungen über die Bild. der Peptone in den Organen. Diss. Rostock, 1890.
145. Nasse: Ueber primäre und sekundäre Oxydation. Ar. P. M. **41.** 378. 1887.
146. Embden u. Amalgia, quoted by von Noorden u. Embden: Einige Probleme des intermed. Kohlenhydratstoffw. C. S. **1906.** Nr. 1. P. 1.

147. Corin u. Ansiaux: Über Phosphorvergiftung. Vierteljahrsschr. f. ger. M. **7.** 80. 1894.
148. Vogel: Ueber die Wirk. des P. auf die roten Blutkörperchen bei Hühnern. Ar. i. P. **10.** 1902.
149. Schwarz: Untersuch. über Diabetes. D. Ar. M. **76.** 234. 1903.
150. Heffter: Beitr. zur Chemie des quergestreiften Muskels, etc. E. A. **31.** 225. 1893.
151. Clerc and Cook: Metab. w. Organ. and Inorgan. Phosph. J. Biol. Chem. V. 151. 1906.
152. Wohlgemuth, J.: Phosphorharn. Z. p. C. 1906.

(β) Oil of Pennyroyal.

The chemical symptoms of poisoning by oil of pennyroyal (1) are, so far as is known, remarkably like those produced by phosphorus. Accurate experiments on dogs showed that general metabolism at first was hardly altered, and then sank about 20 per cent. The cause was decrease in fat metabolism, as was very clearly shown by respiration experiments. The protein metabolism is markedly raised. Leucin and tyrosin have been found in the urine (2), but not always (1). Increase of fat was regularly found in heart and liver (3, 5), but not in the kidney (4).

LITERATURE.

1. Lindemann: Ueber die Veränderungen des Gesamtstoffwech. bei Vergiftung mit Pulegon. Z. B. **39.** 1. 1899.
2. Falck: Ueber Oleum Pulegii. T. M. **4.** 448. 1890.
3. Rosenfeld: Fettbildung. Er. Ph. II. **2.** 50. 1903.
4. Rosenfeld: Stud. über Organverfettungen. E. A. **55.** 179. 1906.
5. Bonanni: Ueber die Herkunft des Fettes bei Pulegonvergiftung. Arch. di farm. sper. **2.** 97. 1903.

(γ) Halogen Narcotics of the Aliphatic Series.

The symptoms are so simliar to those of phosphorus-poisoning in certain points that we may conclude they are produced in the same manner.

(δ) Arsenic.

Small Therapeutic Doses.—In spite of its frequent and effective use in practice, the cause of the therapeutic action of arsenic is but little understood. In numerous instances a marked rise in weight is noticed, and is usually attributed to the increased appetite produced by the drug. This cannot, however, be the only cause, as it has been observed to occur with a constant diet in the exact experiments of Henius (1) with atoxyl (meta-arsenic acetanilide). Doubtless the growth of the bones and fatty tissues (2), and the remarkable increase in hæmoglobin and erythrocytes (5, 31), are partial expressions of the specific action of arsenic. The well-known arsenic-eating horses and men in Styria also point to a specific action, as it would be a bold assumption to suppose that they had all previously suffered from loss of appetite.

Henius made the earliest experiments on gaseous metabolism. By the Geppert-Zuntz method he was able to show that there was no change in the net values of oxygen intake and CO_2 output in a patient under treatment with atoxyl whose weight, which was previously rising, increased during the course of the cure by 2·5 kilogrammes (five pounds). In all these experiments the Geppert-Zuntz method should be controlled by some other, as a very gradual decrease in the gaseous interchange could not be detected.

Protein metabolism in animals on very small doses is distinctly diminished (7). A sheep put on about 0·8 gramme nitrogen daily, and assimilation was improved (6). In other cases the nitrogenous metabolism was unaffected (8, 9). In man a tendency to increase in weight has always been noted. Ewald and Dronke's experiments are not clear, as the arsenical waters they used also contained iron, but their results pointed to the same direction (24).

Toxic Doses.—Chittenden and Cummins have carried out the only experiments on gaseous interchange as far as I know. They found in rabbits the CO_2 output somewhat decreased by daily doses of 35 milligrammes arsenic. Usually, however, there is an increase in protein metabolism both in starved and fed animals (7, 11, 12).

In a very short time (a few hours) the liver is free from glycogen (14 to 20), but the muscle glycogen is more resistant. The liver glycogen disappears before there is any appreciable increase in fat, which, considering the theory as to the interchangeability of fat and glycogen, is not without significance. Poisoned animals fed on sugar failed to form further glycogen, but glycosuria was much more easily induced (16) than usual. The sugar content of the liver and blood was not increased according to the earlier experiments, and the more recent ones have given uncertain results. New experiments are much needed, especially as glycosuria is infrequent in spite of the rapid disappearance of glycogen (22). It is stated that neither curare nor diabetic puncture produce glycosuria in poisoned animals, the cause being probably absence of glycogen.

The CO_2 content of the blood is much decreased by toxic doses (23). The cause of this is not to be found in an increased ventilation of the blood, as the respiration is mostly gentle and shallow, but the excretion of CO_2 due to the occurrence of acid bodies. Of the organic acids, lactic acid has been found in increased amounts ; in dogs this was the optically inactive acid of fermentation, the zinc salt of which loses 17·88 per cent. water of crystallization on drying, whereas sarcolactate of zinc loses 12·9 per cent. This is an isolated instance, and must, among other things, depend upon the kind of animal, as optically active lactic acid has been found in the blood of cats. The increase is not inconsiderable, and may amount to 150 per cent. (normal blood 0·042 per cent., after poisoning 0·113 per cent. on the average).

The origin of the lactic acid is obscure. Sarcolactic acid is constant in blood, muscle, and liver. In the fresh livers of cats, dogs, and rabbits, Morishima found 0·113 per cent. on the average ; in cats poisoned with arsenic the fresh liver contained 0·168 per cent.—an increase of about 50 per cent. In the muscles the figures are 0·388 per cent. as against

0·314 per cent. normal (18). A special increase occurred in the kidneys (0·111 per cent. to 0·385 per cent.) and the intestinal wall (0·161 per cent. to 0·422 per cent.).

In some very careful experiments, Morishima tried to show a relation between the increase in lactic acid and the decrease in carbohydrate. He first estimated the amounts of each in fresh livers and in livers which had been kept for some time.

Number of Experiment.	*Animal.*	*Glycogen.*		*Sugar.*		*Zinc Lactate.*		*Increase.*
		Fresh.	Later.	Fresh.	Later.	Fresh.	Later.	
		Per Cent.	Per Cent.	Per Cent.	Per Cent.	Per Cent.	Per Cent.	
1	Cat	3·87	1·84	0·91	2·20	0·246	0·217	—
2	Cat	6·71	5·45	1·81	2·68	0·159	0·676	1 : 4·2
3	Rabbit	9·80	5·28	0·41	3·62	0·230	0·283	1 : 5·6
4	Dog	3·45	0·30	1·17	3·84	0·191	0·833	1 : 4·2
5	Cat	5·81	3·68	1·42	2·84	0·181	0·313	1 : 1·7

A comparison of the decrease in carbohydrate (calculated as sugar) with the increase in lactic acid shows :

	Number of Experiment.				
	1.	2.	3.	4.	5.
Decrease in carbohydrate ..	0·97	0·520	1·820	0·830	0·940
Increase in lactic acid	0·00	0·517	1·053	0·636	0·132

As the carbohydrate disappeared more rapidly than lactic acid was formed, it suggests that if carbohydrate usually forms lactic acid, it is not all converted into that substance, or that the lactic acid is further decomposed. By digesting grape-sugar or glycogen with liver extract, after the formation of fermentation-lactic acid, it was found that CO_2 was developed (4). In Morishima's experiments the lactic acid was about 65 per cent. of the fermentation form and 35 per cent. sarcolactic, and as fresh liver contained none of the fermentation-lactic acid, it is probable that it is first formed during the digestion experiment.

These observations show that it is very possible that lactic acid formation may take place *intra vitam* at the expense of the glycogen. But there is no more definite evidence. Possibly the lactic acid may arise from some quite different substance—*e.g.*, albumin. Nor can anything more definite be said as to the relationship between the fermentation acid and sarcolactic acid. In the urine of dogs and rabbits poisoned with arsenic, Araki found none of the constituents of bile, but an acid the properties of which correspond to neither lactic acid, as, though its water of crystallization was 13·14 per cent. (nearly the same as sarcolactic), it was optically inactive.

Post-mortem examinations of cases of arsenical poisoning show fatty infiltration of the liver.

The synthesis of hippuric acid is not affected (21), and no abnormal quantities of phenol are formed from benzol (13).

Theory of Arsenic-Poisoning.

Though cases of arsenic-poisoning, either in man or in experimental animals, are not numerous, a general resemblance of the symptoms to those of phosphorus-poisoning can be established. In both cases small doses produce increased growth, large doses all the signs of decreased oxidation : marked disturbance of the liver—sometimes in rabbits, and often in dogs, there is jaundice with bile pigments in the urine—increase of fat in certain organs, increase in protein metabolism, rapid disappearance in glycogen, occurrence of lactic acid in large quantities, and decreaed alkalinity of the blood. No doubt other symptoms resembling those of phosphorus-poisoning could be found—as, for instance, the occurrence of amino-acids in the urine. It is very probable also that the total oxidation is diminished. A primary damage to the oxidative powers of the cells may, therefore, correctly be assumed, especially as estimations of the hæmoglobin and other blood examinations have failed to show any toxic changes in the blood. Wiley Jones (25) notes that arseniuretted hydrogen acts differently to the other arsenic compounds, causing a rapid dissolution of the hæmoglobin and disintegration of the erythrocytes, and also marked degenerative changes in the kidneys. The observation that the oxidation of benzol is not interfered with is not really opposed to these conclusions, owing to the ambiguous nature of the result.

LITERATURE.

1. Henius : Beitr. zur Arsenbehandl. der Chlorose. Diss. Giessen, 1902.
2. Giess : Über den Einfl. des Arsen auf den Organismus. E. A. **8.** 175. 1877.
3. von Noorden : Die Bleichsucht. 1898.
4. Ekunia : Ueber die Ursache der sauren Reaktion der tier. Gewebe nach dem Tode. J. p. C. **21.** 478. 1880.
5. Reich : Ueber die Wirk. des As auf die roten Blutkörperchen. Diss. München, 1899.
6. Weiske : Über den Einfl. von Arsenbeigabe auf die Ausnutz. des Futters sowie auf den Stickstoffumsatz. J. f. Landwirtsch. **23.** 317. 1875.
7. Imjanitoff : Ueber den Einfl. der arsenigen Säure auf den tier. Stoffwechsel. Ma. **1901.** 751.
8. von Böck : Über die Zersetzungen des Eiweisses unter dem Einfl. von Morphin, etc. Z. B. **7.** 418. 1871 ; **12.** 512. 1876.
9. Fokker, cit. by Voit : Handb. d. Physiol. d. Stoffw. **1881.** P. 182.
10. Chittenden and Cummins : cit. by Ma. **17.** 342. 1887.
11. Gäthgens : Ueber die Steigerung des Stickstoffkreislaufs durch Arsenpräparate. C. m. W. **1875.** 529. **1876.** 833.
12. Kossel : Zur Kennt. der Arsenwirkungen. E. A. **5.** 128. 1876.
13. Nencki u. Sieber : Ueber eine neue Methode die physiol. Oxydation zu messen, etc. Ar. P. M. **31.** 319. 1883.
14. Rosenbaum : Ueber den Kohlenhydratbestand des tier. Organismus nach Vergift. mit Arsen, etc. Diss. Dorpat, 1878.

15. Saikowsky: Ueber die Fettmetamorph. der Organe nach innerl. Gebrauch von As, Sb und P-Präparaten. Ar. p. A. **34.** 73. 1865.
16. Luchsinger: Physiol. und Pathol. des Glykogens. Diss. Zürich, 1875.
17. Konikoff: Ueber den Einfl. gewisser Agentien auf die Menge des Glykogens in der Leber. Ma. **1876.** 198.
18. Heffter: Beitr. zur Chem. des quergestreiften Muskels mit Berücksichtigung der Totenstarre und einiger Vergiftungen. E. A. **31.** 225. 1893.
19. Benz: Ueber den Kohlehydratstoffw. beim Kaninchen nach akuter Vergift. mit arseniger Säure. Diss. Würzb., 1897.
20. Morishima: Ueber das Vorkom. der Milchsäure im tier. Organismus mit Berücksichtigung der Arsenvergift. E. A. **43.** 217. 1899.
21. Oé: Zeitschr. d. med. Ges. Tokio. **13.** 847. Cit. by Katsuyama, Z. p. C. **34.**
22. Araki: Beitr. zur Kenntnis der Einwirk. von Phosphor und arseniger Säure. Z. p. C. **17.** 311. 1893.
23. Meyer: Über die Alkaleszenz des Blutes. E. A. **17.** 304. 1883.
24. Dronke u. Ewald: Über den Verlauf des Stoffwech. bei längerem Gebrauch eines Levico-Arsen-Eisen-Wassers. B. k. W. **1892.** Nrs. 19, 20.
25. Wiley Jones: J. Am. Med. Assoc., xlviii., p. 1099. 1907.

(ε) Antimony.

Poisoning by antimony is relatively uncommon, and thus has been little studied experimentally. The literature consists of reports of cases.

Large doses diminish the CO_2 output in starved rabbits [Chittenden and Cummins (1)]. Protein metabolism is unaltered in fed dogs by 1 to 1·5 grammes of oxide of antimony given by the mouth [Chittenden and Blake (2)], but in starved animals it is markedly raised (30 per cent.) [Gäthgens (3)]. After intravenous injection the CO_2 in the blood diminishes (4), and rapid disappearance of glycogen and fatty infiltration of the organs has been observed (5). Other results as to glycogen were obtained by Chittenden and Blake (2).

These sparse communications show that the action resembles that of arsenic.

(ζ) Iron.

Iron has already been thoroughly considered as regards the formation of Hb [Magnus-Levy (8)]. The therapeutic use of iron has nothing to do with this function, as iron hunger, with all its serious consequences to nutrition (9), plays no part in pathology. The reason is that other drugs and other methods may often effect the same cure as iron.

The frequent use of iron is in glaring contrast to the sparsity of our knowledge as to the metabolic changes which it produces. In small doses it acts similarly to arsenic—at least, it increases blood formation, and at the same time "improves nutrition" (10). Probably this effect is the result of the same action on metabolism as the increased blood formation—namely, overcompensation for the slight decrease in the oxidizing capacity of the cells induced by iron, as by high altitudes.

In one experiment on a dog (11) the nitrogen balance remained unchanged when 0·3 to 0·5 gramme (5 to 7½ grains) of perchloride of iron was given in very dilute solution. A fall was observed in another case, but there were objections to the method of experiment (7).

There is no case of poisoning by iron taken by the mouth, as too little is absorbed. Large doses act as intestinal irritants.

Subcutaneously larger doses produce severe general toxic symptoms; the CO_2 in the blood falls (6); hence we may conclude that an acidosis occurs as with arsenic, which in this case also may be attributed to diminished oxidation.

It would be of interest, with a view to throwing some light on the mode of action of iron, to compare the metabolism under non-toxic subcutaneous doses with that under similar doses of phosphorus and arsenic.

LITERATURE.

1. Chittenden and Cummins: cit. by Ma. **17.** 343. 1887.
2. Chittenden and T. A. Blake: Einfl. von Antimonoxyd auf den Stoffwechsel. Cit. by Ma. **17.** 403. 1887.
3. Gäthgens: Zur Kenntnis der Antimonwirkungen. C. m. W. **1876.** Nr. 18.
4. Meyer: Über die Alkaleszenz des Blutes. E. A. **17.** 304. 1883.
5. Saikowski: Ueber die Fettmetamorph. der Organe nach innerl. Gebrauch von As, Sb und P-Präparaten. Ar. p. A. **34.** 73. 1865.
6. Meyer u. Williams: Ueber akute Eisenwirkung. E. A. **13.** 70. 1880.
7. Rabuteau: C. rend. **86.** 1169. 1876.
8. Magnus-Levy: This book. Vol. **1.**
9. Hösslin: Ueber Ernährungsstör. infolge Eisenmangels in der Nahrung. Z. B. **18.** 612. 1882.
10. Von Noorden: Die Bleichsucht. 1898.
11. Munk: Ueber den Einfl. des Alkohols und des Eisens auf den Eiweisszerfall. D. A. **1879.** 163.

D.—MERCURY, URANIUM, CHROMIUM, CANTHARIDES.

These poisons are grouped together merely because they produce certain symptoms in common, such as fatty changes in the organs, nephritis, disappearance of glycogen, and regular glycosuria, without such clear proof of a preceding hyperglycæmia as can be obtained with other poisons.

The nephritis and glycosuria, which are prominent symptoms, distinguish this group from that of phosphorus, arsenic, and antimony, in which they are insignificant. It cannot definitely be decided whether differences also exist in the protein metabolism.

1. Mercury.

The action of very small doses is analogous to that of arsenic and phosphorus—increase in fatty tissue and the production of erythrocytes. This has been observed in cats, dogs, and fowls, in which very small doses of sublimate were given for months (1). The increased blood formation has been observed both in man and in healthy and diseased animals (2 to 9).

In starved dogs small doses of sublimate produce no alteration in the gaseous interchange (10) or in the protein metabolism (7, 11, 12). Noël Paton, however, found a slight rise in nitrogen metabolism in a dog (13).

Mercury must be given in large doses to produce the same effect on protein metabolism as arsenic, antimony, and phosphorus, but this is impracticable, as the intoxications are complicated by severe nephritis and albuminuria, so that the protein metabolism cannot be estimated. Possibly the decreased nitrogen excretion in the urine once observed (14) was due to a retention of end-products consequent on nephritis.

Actually a large increase in the urea (residual nitrogen) in the blood has been found, amounting twice to ten times the normal, as occurs, also, with other bodies which produce nephritis (15 to 17). The increase in nitrogen in the blood does not balance the decrease in the urine, so probably some is retained in the tissues. Very frequently—in fact, almost invariably—sugar is found in the urine (18 to 21). This is due to the hyperglycæmia, which has been found in a high degree by Richter (22), but not by Kissel and others (23). The point cannot be certainly decided. There is always a marked disappearance of glycogen.

There are no experiments as to the occurrence of lactic acid in the urine.[1]

Special changes occur in the blood and kidneys. In distinction to phosphorus and arsenic, mercury in large doses is an intense blood poison (24, 25). Noël Paton demonstrated a marked diminution in the erythrocytes.

The kidneys show remarkable deposits of lime (27 to 29). Experiments undertaken to explain its presence showed that in 50 per cent. of the cases there was an absolute increase in the calcium content of the kidneys, whereas the blood and urine were practically free (30). Prévost states that he has found a slight diminution in the amount of calcium in the bones.

Fatty infiltration of the organs has often been described.

In an accurate experiment the alkalinity of the blood was found to be decreased (26, 31).

The analogy to phosphorus-poisoning consists in the action of small doses on the blood formation and metabolism, and of larger doses on fatty changes, disappearance of glycogen, etc. The action on protein metabolism is apparently anomalous ; if it could be determined that the difference is only quantitative, mercury would have to be removed from this group.

The specific action of large doses is on the kidneys, the erythrocytes, and the frequent appearance of glycosuria.

LITERATURE.

1. Schlesinger : Über die Wirk. lange Zeit fortgegebener kleiner Gaben Quecksilbers auf Tiere. E. A. **13.** 317. 1881.
2. Wilbouchewitsch : De l'infl. des prép. mercur. sur le sang. Ar. P. **1874.**
3. Keyes : L'action toxique et thér. du Mercure. 1875.
4. Liègeois : Des résultats obtenus avec les inject. soucutanées de sublimé à petites doses dans l'étude de la syphilis. Ga. H. **1869.**
5. Bennet : On the Action of Mercury on the Biliary Secretion. 1874.
6. Robin : Thèse de Paris. **1880.**

[1] W. E. Dixon ("Pharmacology," 1906, p. 381) states that the lactic acid production is increased, and attributes to this the decreased alkalinity of the blood. The gaseous exchange is also diminished.

7. Cederkreutz: Beitr. zur Kenntnis des Stoffw. in der Frühperiode der Syphilis, etc. Diss. Breslau, 1902.
8. Galliard: De l'action du mercure sur le sang, etc. Ar. g. m. **1885.** 527.
9. Biegánski: Ueber die Veränderungen des Blutes unter dem Einfl. von pharm. Gaben von Hg-Präparaten. Ar. D. S. **24.** 43. 1892.
10. Schröder: Der Stoffw. der Kaninchen bei akuter Quecksilbervergiftung. Diss. Würz., 1893.
11. Böck: Ueber die Zersetz. des Eiweisses unter dem Einfl. von J und Hg. Z. B. **5.** 393. 1869.
12. Berg: Ueber die Wirk. der sog. Alterantien insbes. des Quecksilbers auf den Stoffwechsel. Diss. Rostock, 1881.
13. Noël Paton: The Nature of the Relationship between Urea Formation and Bile Secretion. J. A. and P. **20.** 520. 1887.
14. Bruck: Ueber den Einfl. des Sublimats auf den Stoffwechsel. Diss. Berlin, 1887.
15. Doléris et Butte: Sur l'intox. par le sublimé corrosif. Nouv. arch. d'obst. et gyn. **1886.** Nr. 12.
16. Gürber u. Guttenberg: Über den Stoffw. bei akuter Hg-Vergiftung. Mü. m. W. **1895.** 1.
17. Strauss: Die chron. Nierenentzündungen in ihrer Einwirkung, etc. 1902.
18. Saikowsky: Ueber einige Veränderungen, welche das Quecksilber im tier. Organismus hervorruft. Ar. p. A. **37.** 346. 1866.
19. Mering: Ueber die Wirk. des Quecksilbers auf den tier. Organismus. E. A. **13.** 86. 1881.
20. Graf: Glykosurie bei Quecksilbervergift. Diss. Würz., 1895.
21. Heilborn: Über Wirkung subkutaner Sublimatinjektionen. E. A. **8.** 361. 1878.
22. Richter: Zur Frage des Nierendiabetes. D. m. W. **99.** 841.
23. Kissel: Über den Glykogengeh. der Kaninchenleber. Diss. Würzb., 1894.
24. Kaufmann: Die Sublimatintoxikation. 1888.
25. Polotebnow: Über die Wirkung der Quecksilberpräparate. Ar. p. A. **31.** 1864.
26. Peyron: Über die Schwankungen der respir. Kapaz. des Blutes. Thèse de Paris. **1891.**
27. Königer: Exper. Beitr. zur Kenntnis der akuten Hg-Vergiftung. Diss. Würzb., 1888.
28. Prévost et Frutiger: Sur l'intoxication par le mercure, son action, etc. Rev. méd. de la Suisse rom. **1882.** 11, 12.
29. Carvonen: Ueber den Einfl. des Quecksilbers auf die Nieren. D. Zt. **5.** 113. 1898.
30. Jablonowsky: Ueber die Einwirk. des Hg auf den tier. Organismus. Diss. Berlin, 1884.
31. Meyer: Über die Alkaleszenz des Blutes. E. A. **17.** 304. 1893.

2. Uranium.

According to Chittenden and Cummins (1), the CO_2 output in rabbits poisoned with uranium is somewhat raised. They also noticed a rise in temperature. Small doses in dogs have no effect; larger ones raise the protein metabolism—increase of N, H_2SO_4, P_2O_5. The powerful action of uranium on the kidneys prevents more exact estimations [Chittenden and Lambert (2)]. These observers also found a rapid disappearance of glycogen in rabbits. Glycosuria is almost invariable; as it does not occur in starving animals, it cannot be placed in the category of phlorizin glycosuria (3 to 8). Moreover, hyperglycæmia is found almost without exception during, and not before, the glycosuria (10), the figures being 0·1791 to 0·261 per cent. [Meyner (9)], and 0·2 per cent. [Fleckseder]. Animals poisoned with uranium differ, too, from

phlorizinized animals, as in these the hyperglycæmia persists after extirpation of the kidneys. Fatty changes in the organs have been regularly found. Lactic acid has not been noted in the urine.

3. Chromium.

This closely resembles uranium in producing fatty infiltration in the liver and heart (11), but not in the kidneys; nephritis and glycosuria are almost invariable (12 to 15). Hyperglycæmia does not occur after extirpation of the kidneys. The nephritis of chromium prevents, or diminishes, the glycosuria produced by phlorizin or diuretin (16, 17).

4. Cantharides.

The prominence of the symptoms of nephritis and fatty infiltration after cantharides accounts for its inclusion in this group. With regard to the nephritis, it has been shown that the urine is alkaline (18). The immunity of certain animals to this poison has long been recognised. The fatty infiltration is said to affect the liver, but not the heart (19); the kidneys contain less fat (20). All these organs are particularly watery.

Glycosuria is not uncommon in rabbits (21), whereas other forms of glycosuria (phlorizin, caffeine) are diminished by cantharides; hyperglycæmia has not been recognised.

5. Lead, Platinum, Copper, Zinc.

The effect of these very unabsorbable metals on metabolism is but little understood. In starved rabbits copper raises the CO_2 output [Chittenden and Cummins (1)]. Small doses increase the blood formation in anæmia (22, 23), and the same has been observed in healthy animals (5), though not invariably (25, 26).

Zinc is said to have a therapeutic value as a blood-forming substance (27, 28), but experiments on rats have only yielded negative results. Severe chronic poisoning with lead frequently produces anæmia (28). The erythrocytes are destroyed and the urinary urobilin increased.

Acute poisoning by subcutaneous injection of lead decreases the CO_2 expired (31), and also that of the blood (32). The latter fact has also been observed with platinum and copper (30). These two metals also decrease considerably the oxidation of benzol to phenol (34).

The protein metabolism in chronic lead-poisoning in man has often been investigated, but not under wholly unexceptionable conditions. Sometimes a considerable rise has been noted (36), but this has not been confirmed by further observations on sheep (37), dogs (38), and men (39). A diminution in urinary nitrogen has been stated to be the usual occurrence by Bucco and others (40 to 43), but Götze states that it is increased during the attack. It may be taken as certain that in the presence of certain predisposing conditions lead conduces to the development of gout (35). Changes in the urea output in dogs poisoned by lead have not been noted. Alimentary glycosuria is easily set up (eleven times in twenty-one cases) (24).

LITERATURE.

1. Chittenden and Cummins: Einfl. einiger organ. und anorganischer Stoffe auf den Gaswechsel. Ma. **17.** 342. 1887.
2. Chittenden and Lambert: Untersuchungen über die physiologische Wirkung der Uransalze. Z. B. **25.** 513. 1888.
3. Léconte: Résumé des expér. sur l'acétate d'uranium. G. m. P. **1854.** 196.
4. Woroschilsky: Ueber die physiol. Wirk. des Urans. Diss. Dorpat, 1889.
5. Giudiceandrea: Ueber die hämatogene Wirk. des Kupfers. P. **1900.** 23.
6. Fleckseder: Ueber Hydrops und Glykosurie bei Uranvergiftung. E. A. **56.** 53. 1906.
7. Cartier: Glycosuries toxiques. Thèse de Paris. **1891.**
8. Lépine: Les glycosuries toxiques. Ar. m. ex. **15.** 129. 1903.
9. Meyner: Der Kohlenhydratverbrauch bei Uranvergiftung. Diss. Würzb., 1898.
10. Lépine et Boulud: Ueber die Abwesenheit von Hyperglykämie bei Uranylvergiftung. Re. m. **1904.** H. 1-3.
11. Rosenfeld: Über Organverfettungen. E. A. **55.** 179. 1906.
12. Kossa: Chromsäurediabetes. Ar. P. M. **88.** 627. 1902.
13. Lohr: Akuter Chromvergift. mit spontaner Glykosurie. B. k. W. **41.** 749. 1904.
14. Rössle: Wirk. der Chromsäure. D. Ar. M. **75.** 569. 1904.
15. Pal: Glykosurie bei Chromvergiftung. W. m. W. **1902.** 846.
16. Hellin u. Spiro: Ueber Diurese. E. A. **38.** 368. 1897.
17. Richter: Über die Beziehungen zwischen Nieren und Glykosurie. Z. M. **41.** 160. 1900.
18. Ellinger: Beziehungen zwischen der Giftwirk. des Kantharidins auf die Nieren und der Reaktion des Harns. Mü. m. W. **1905.** Nr. 8.
19. Rosenfeld: l.c. (11).
20. Rosenthal: Fettbildung. D. Ar. M. **78.** 94. 1903.
21. Richter: Zur Frage des Nierendiabetes. D. m. W. **1899.** Nr. 51.
22. Cervello u. Barabini: cit. by Wolf (26).
23. Cervello u. Scarpinato: cit. by Wolf (26).
24. Rosenberg: Ueber das Vorkommen der aliment. Glykosurie bei Gesunden sowie bei einigen Intoxikationen. Diss. Berl., 1897.
25. Iliascheff: Ueber den Einfl. der Salze verschiedener Schwermetalle auf die morph. Zusammensetz. des Blutes, etc. Ma. **31.** 255. 1901.
26. Wolf: Ueber den Einfl. von Kupfer- und Zinksalzen auf die Hämoglobinbild. Z. p. C. **26.** 442. 1898.
27. Savoca: cit. by Wolf (26).
28. Grahé: Ueber die Einwirk. von Zink und seiner Salze auf das Blut und den Blutfarbstoff. A. D. **1893.**
29. Galet: Ueber den Bleisaum und die Veränderung des Blutes bei Bleivergiftung. La clinique. **18.** 281. 1904.
30. Meyer: Über die Alkaleszenz des Blutes. E. A. **17.** 304. 1883.
31. Luchsinger u. Hess: Toxikol. Beiträge. Ar. P. M. **35.** 174. 1884.
32. Peyron: Über die Schwankungen der respirat. Kapazität des Blutes, etc. C. r. S. B. **43.** 835. 1891.
33. Brunelle: Ueber alimentäre Glykosurie bei Bleikolik. Ar. g. m. **1894.** 688.
34. Nencki u. N. Sieber: Ueber eine neue Methode die phys. Oxydation zu messen. Ar. P. M. **31.** 319. 1893.
35. Minkowski: Die Gicht [illegible]
36. Götze: Die Bleiverg[illegible] V. W. G. **22.** 8. 1893.
37. Ellenberger u. Hofmeister: Zur physiol. Wirk. und Deposition der Bleisalze beim Weiderkäuer. Arch. f. Wiss. Tierk. **10.** 3. 1883.
38. Lüthje: Ueber Bleigicht und den Einfl. der Bleiintoxikation auf die Harnsäureaussch. Z. M. **29.** 266; **31.** 112. 1896.
39. Surmont et Brunelle: Über die N-Aussch. bei Bleikolik. Ar. g. m. **1894.** 184.

40. Bucco: Chron. Bleivergiftung, Glykosurie, Harnsäure und oxals. Diathese. Ma. **1900.** 881.
41. Bouchard: C. r. S. B. **1873.** 271.
42. Combemale et Surmont: Ueber die Aussch. des Stickstoffs im Harn bei Bleikolik. C. r. S. B. **42.** 473. 1890.
43. Gaucher: Re. m. **1881.** 877.

VI.—NARCOTICS AND HYPNOTICS.

Under this heading come a large series of bodies of very different chemical constitution which have in common the power of influencing the central nervous system in various ways by means of certain physico-chemical properties (10); the resultant condition of narcosis changes the amount of oxidation to a definite degree.

Besides this, there are certain quantitative and qualitative changes in metabolism which depend, not on the narcosis as such, but on particular properties of the narcotics. These will be dealt with after the changes due to narcosis itself have been considered.

A.—EFFECTS OF NARCOSIS.

1. Gaseous Metabolism.

In deep narcosis, oxidation processes are quantitatively diminished as during sleep, only more markedly. This is the invariable result of animal experiments (no observations on man are known to me) with all narcotics and all methods of estimation. The oxygen intake and carbonic acid output have been investigated for chloral (1, 2), paraldehyde (3), chloroform, alcohol and ether (1), and morphine (1, 5 to 8), and the CO_2 when oxygen was simultaneously administered (9, 12).

The unanimity of the results renders it unnecessary to consider the individual experiments, which are not all of the same value. The decrease in oxidation is shown by the fall of temperature during narcosis, as well as by the gas analyses; in man, the former in ordinary narcosis may reach 0·3° to 1·0° C. It is due to the fact that, owing to paralysis of the thermotaxic centre (11), the increased loss of heat from the surface of the body (due to vaso-dilatation) is not compensated by increased heat production. The question whether narcotics in general directly decrease oxidation is still open. Rumpf denied it on the very inadequate ground that *in vitro* the oxygen disappears from the blood equally rapidly with or without the addition of an anæsthetic. It may be said, in view of prevalent ideas on narcosis, that, since it is produced by an interaction between the narcotic and the cell lipoid, it must set up some damage in the direction of diminished oxidation in all cells in which the lipoid forms part of the centre of metabolic activity. However, we do not know where this takes place, except that it is in the central nervous system.

2. Oxidation of Carbohydrates.

Nebelthau (17), in a very careful research on the influence of certain narcotics on the glycogen content of the liver and muscles, showed that carbohydrates share in the general diminution of oxidizing processes, a fact which had previously only been established by unreliable methods (18). He estimated the glycogen content in the liver and muscles of narcotized animals which had previously been starved. Ten rabbits, after six days' starvation, had 0·1 to 0·3 gramme of glycogen; two animals on this day were given 1·2 to 2·3 grammes of chloral. In twenty-four hours the glycogen content in their livers was from 0·4 to 1·0 gramme, and consequently larger than the controls. Numerous similar experiments on fowls gave similar results. After four to six days' fast, the glycogen content of the liver varied between 0·02 and 0·14 gramme (maximum error, 1 per cent.), of the muscles between 0·03 and 1·8 grammes. On the sixth day, chloral, paraldehyde, chloroform, ether, alcohol, sulphonal, or urethane, were given till sleep ensued. The glycogen content invariably rose far above the maximum found in the controls, reaching 1·7 to 3·1 grammes. These experiments are free from the objection that glycogen may be formed during starvation, as it is used up again under normal conditions, so that only traces are usually found.

If, however, the amount used up is diminished—for instance, through decreased muscular or glandular activity, due to the failure of central stimulation in narcosis—an accumulation occurs. That this view is correct is seen by the fact that Nebelthau (20) found increased glycogen in starved animals after section of the spinal cord. Here, too, may be mentioned the fact that chloral prevents glycosuria when the fourth ventricle is punctured (20). This is because the narcotized brain is not affected by the stimulus of the puncture, and does not, therefore, pass it on. Chloral fails to control the glycosuria of CO-poisoning. In man it has seldom been tried, and the results are not uniform, because an efficient dose cannot be given without harm, or because the glycosuria is otherwise produced (21). Opium or morphine are the only narcotics which will act in this way, and then only in certain cases. Richter (23), from animal experiments which await confirmation, considers that this action is similar to that just described for chloral.

B.—SPECIAL EFFECTS OF INDIVIDUAL NARCOTICS.

These effects, which can be obtained alone by means of non-narcotic doses, are now to be considered, though some—for instance, those of the halogen narcotics—more properly belong to other groups.

1. Chloroform, Chloral Hydrate, Chloralose.

It is possible that chloroform directly decreases oxidation, as a fall in temperature occurs in animals when heat loss from the skin is prevented. Sometimes it may be due to the relaxation of muscular tone. It has also been shown that with chloroform narcosis, but not with ether, less benzol than normal is oxidized to phenol (14, 15). Although the explanation of this is not clear, the specific non-narcotic effects of chloroform have been well established by numerous observations (79).

(*a*) *Protein Metabolism.*

The total protein metabolism is increased during chloroform narcosis, as shown by experiments on a starved dog (30) and one in nitrogenous equilibrium (31). This is not due to the narcosis, for chloroform water in very small, non-narcotic doses gives the same results (31 to 35). Chloral hydrate acts similarly in narcotic and in smaller doses (31, 36 to 38). At the outset, under some circumstances, a diminished output of nitrogen may occur, but this is by no means a usual event (32). There is only one somewhat inadequate research on the influence of chloralamide [T. Gordon (39)]. Most of the nitrogen in rabbits is excreted as urea. In dogs this does not occur. With the exception of an insignificant increase in ammonia excretion, the greater part appears as a special body which contains nitrogen and sulphur, and gives no biuret reaction (*vide infra*). Dixon (100) states that most of the nitrogen is excreted as alloxuric bodies.

(*b*) *Excretion of Chlorides and Phosphorus.*

The excretion of these substances shows a corresponding increase to that of the nitrogen. With regard to the former, Kast (41) has made the important observation that dogs poor in chlorides after the repeated administration of chloroform showed an increased output. Perhaps this was a secondary effect of the severe general damage inflicted on the organism by the repeated narcosis, to which the loss of weight also was due. Kast does not consider this rise in chloride excretion analogous to a similar observation of Forster's (42) on animals deprived of their chlorides by starvation. At the same time, bilirubin appears in the urine in dogs, possibly owing to a breaking down of blood-corpuscles which has often been observed *in vitro*, but seldom *in vivo*. Urobilin is present in fair amount in the urine of men three to four days after chloroform narcosis without the occurrence of any loss of blood elements (44).

(*c*) *The Excretion of Sulphur.*

The total sulphur excretion is increased in correspondence with the protein (34 to 38, 69). Either immediately or after a few days a change

in its composition occurs, the unoxidized sulphur increasing considerably at the expense of the sulphates (chloral hydrate and chloroform in man and dogs). Kast and Mester's figures are very instructive :

Percentage of Unoxidized Sulphur in the Total Excreted.

Before Narcosis.	*After Narcosis.*
12·5	.. 20·8
16·6	.. 30·8
14·9	.. 32·2
10·4	.. 20·0

The percentage of unoxidized sulphur varies between 15 and 18 (50 to 52). Observations for longer periods show that the difference tends to disappear. The explanation of this depends on the conception we form of the origin and significance of the neutral sulphur. Only the first steps towards an experimental basis for the various phenomena have been made ; practically all the work on this subject remains to be done by future investigators. Some have considered the neutral sulphur as a forerunner of the oxidized, and its increase as the symptom of a general diminution of the power of oxidation in the organism. As this disability was not observed in dogs after administration of amylene hydrate, Harnack considered the Cl in the halogen bodies as responsible, and proved the correctness of the assumption by giving a combination of chloral and alkali, hoping by means of the latter to neutralize the chlorine which would eventually be liberated in the body. Sodium carbonate, when administered alone, produced no change in the composition of the sulphur—this was in contradiction to the results of similar experiments by Jawein (53) and Ken Taniguti, who, however, used much larger quantities of alkali—and in combination with chloral hydrate the same effect was obtained. The figures, however, varied so much for individual days and for longer periods that it is impossible to consider Harnack's results as final. Benedikt put forward another view. As a result of a number of very careful experiments on men, and a critical estimate of the available data, he considered it very probable that normally the unoxidized sulphur is not usually the antecedent of the sulphates (or only to a slight extent), and that the amount excreted is, in contradistinction to that of the latter, comparatively constant, and does not depend on that of the urea any more than does the excretion of uric acid. He came to this conclusion from the fact that the increase of unoxidized sulphur is usually given in percentages, and does not denote an absolute amount. Thus, a relative increase in the unoxidized sulphur, with unchanged total sulphur excretion, only shows a diminution in the formation of sulphates and of protein metabolism, not a general decrease in oxidation processes. These two latter processes do not by any means run parallel to one another. Diminished fat katabolism alone can lead to an absolute increase in neutral sulphur at the expense of the sulphates, just as decreased carbohydrate katabolism leads to the formation of acetone ; increased fat katabolism, on the other hand, leads to a decrease in the neutral sulphur (524). Hence the increase in the neutral sulphur after the halogen narcotics—which is an absolute increase—must be due

to diminished oxidation of fats. That this occurs in narcosis seems indubitable in view of our general knowledge of the oxidation processes. The results of the investigations so far carried out do not definitely indicate whether the decreased oxidation of fat, or the generally diminished oxidative power, is actually the cause of increased excretion of sulphates, or whether there is some other entirely different reason for this phenomenon.

It is also undecided whether the neutral sulphur is in the same form as that found in normal urine. Harnack (55) has isolated a substance from the urine of dogs fed upon meat, after the exhibition of chloral hydrate, similar to that which is met with after phosphorus-poisoning. The only characteristics of this body are that it is precipitated by phosphotungstic acid, contains sulphur and nitrogen, and gives a characteristic smell on dry distillation. After chloroform narcosis in man a sulphur-containing body has also been isolated, which is normally present in very small quantities or not at all. This substance has not been obtained in a pure state. Urine treated with 10 per cent. caustic soda at 100° C. gave a deep black in the presence of lead, but the sulphur could not be separated even after several hours' boiling. Here, again, is a wide field for future investigators.

(*d*) *Acidity of the Urine.*

Titration with alkalis showed a high degree of acidity [Kast and Mester].

Before ..	22·4	27·0	20·7	15·0	20·0	16·5
After ..	38·0	42·5	28·0	43·0	40·0	48·0

Lactic and oxybutyric acids could not be recognised.

Probably there is an increase in volatile fatty acids, which has been shown to occur at any rate after alcohol narcosis [Thomas].

(*e*) *Glycosuria.*

Although, as a rule, in narcosis the carbohydrate metabolism is decreased, occasionally—especially after chloroform—there is a sudden clearing out of the glycogen depots (19), and the consequent hyperglycæmia (58) is followed by glycosuria (56, 57). After chloral, sugar only appears in the urine when the dosage is large (59). The cause of the glycogenic change is probably in some cases a diminished oxygen supply, due to shallow breathing and poor circulation. Manchot's observation that chloralamide is occasionally the cause of a sort of diabetes in man is explained by Naunyn (72).

An alimentary glycosuria is comparatively easily produced after chloroform narcosis (80).

(*f*) *Acetonuria.*

Acetone often occurs in the urine almost immediately after the chloroform administration, and in diabetes occasionally coma super-

venes (91 to 93). Attention was first called in England to cases of "delayed chloroform-poisoning" by Guthrie (94) in 1894, who reported nine cases; and Becker (91) in the following year reported similar cases in which acetone was found to be present in the urine. The main features of the reported cases are advanced fatty changes in the liver, heart, and kidneys, the presence of acetone in the urine, and death occurring some hours or days after the administration of chloroform. The amount of anæsthetic administered has not in all cases appeared to influence the severity of the condition. Guthrie believes that there is generally an antecedent degeneration in the liver. An exhaustive account of this condition was given by Stiles and Macdonald (95) in 1904, and cases have since been noted by Hubbard (96), Brackett, Stone, and Low (97) in America, and by Beesly (98), and Telford and Falconer (99) in this country.

Beesly finds that both chloroform and ether produce a temporary acute acetonuria, that produced by ether being less likely to produce symptoms of acidosis and death, owing to the fact that the excretory power of the kidney is undamaged. Alkalis mitigate the toxic symptoms. Acute previous acetonuria, he thinks, adds considerably to the risk of a fatal result, especially when the anæsthetic is chloroform.

(*g*) *Alkalinity of the Blood.*

In a dog under deep chloroform narcosis, no decrease was found in the amount of CO_2 which could be obtained from the blood by extraction (70), but the alkalinity to titration was less (60, 61). The cause of this striking difference is not certain. Possibly owing to the feeble respiration, the CO_2 tension in the blood and tissues is increased, and this may mask the normal alkalinity in cases of chronic acidosis; only then it is remarkable that the CO_2 content is not changed. Most probably the acidosis is also the cause of the damage to the erythrocytes, as shown by the presence of bilirubin and urobilin (62).

(*h*) *Fatty Changes in the Organs.*

A single chloroform narcosis, as a rule, produces intense fatty changes in the organs, especially in the heart (43, 71) and its ganglia (45), and in the liver (46 to 48).

Microscopically, the kidneys appear fatty, but chemical analysis shows no increase in fat.

Rubow's analyses give the following composition of fats:

	Ethereal Extract.	*Lecithin.*	*Fat.*
	Per Cent.	Per Cent.	Per Cent.
Normal heart	12·23	8·01	4·21
Chloroform heart	13·48	8·60	4·88
,, ,, ...	14·62	8·91	5·71

The fatty change is not dependent on the narcosis, as it occurs after small subcutaneous injections (49).

The chemical symptoms of chloroform-poisoning are thus very analogous to those of prussic acid, phosphorus, and the poisons which decrease the oxidative power of the cells. It is very desirable that lactic acid and other products of incomplete oxidation should be sought for in these cases.

2. Ether and Paraldehyde.

Narcotic doses do not influence protein metabolism. The alkalinity of the blood has been thoroughly studied by Thomas. Subcutaneous injections in rabbits do not influence the CO_2 content. Kraus's case of a marked fall in CO_2 is explained by Thomas as due to special idiosyncrasy. Inhalation in dogs causes a rise in CO_2 and a fall in O_2, the alkalinity to titration remaining unchanged. Analyses of the blood gases in man are in complete agreement with the findings in animals.

3. Amylene Hydrate.

The protein metabolism and the total sulphur, chlorine, and phosphate excretion dependent thereon are considerably decreased by large medicinal doses in man and in animals (63). The cause cannot be decreased absorption of food-stuffs. No change in composition of the sulphur bodies has been observed.

4. Sulphonal and Trional.

Schaumann's (64) careful research upon himself shows that large medicinal doses do not alter protein metabolism. The older experiments on dogs are inadequate (65, 66). Very large doses eventually produce disintegration of the blood and the appearance of hæmatoporphyrin, and peculiar pigments in the urine (73, 74). Garrod and Hopkins were unable to find any iron in the urine (78). No abnormal coloration of the urine occurs, as hæmatoporphyrin is present as a chromogen. Careful investigations have been made without throwing much light on this phenomenon (75 to 77).

5. Urethane.

Chittenden's (67) experiments on man show that small doses of urethane decrease protein metabolism, large ones increase it.

6. Veronal.

Veronal does not raise the protein metabolism (68). The experiments do not appear to me to show any nitrogen-sparing effect, especially in the absence of an analysis of the fæces.

7. The Morphine Group.

Two experiments on men showed that therapeutical doses of morphine do not influence the gaseous interchange (22). Experiments on animals with morphine (4), codeine phosphate (24), peronine, and dionine (25), gave varying results according to the motor conditions produced. There was no indication of a primary metabolic disturbance.

A dog in nitrogenous equilibrium after a small dose showed a decrease of protein metabolism of about 6 per cent. (81). Another experiment in which the dose was 0·1 gramme per kilogramme showed a remarkable increase in this and in the phosphorus excretion, both when the dogs were in nitrogenous equilibrium and when they were starved (about 100 per cent. in this case) (82). A rapid disappearance of glycogen has been observed.

Glycosuria may appear in severe cases where the oxygen supply is interfered with. It has been compared to the asphyxial glycosuria, but possibly there is another connection. Alimentary glycosuria is easily produced in morphine-takers (80). In cases of chronic poisoning severe nutritional disturbances occur. Apparently these changes are not mainly due to a direct influence of the poison on metabolism, but are secondary, and due to the anorexia produced by gastro-intestinal derangements (83).

8. Alcohol.

As the changes in the poisons introduced into the body will not be dealt with in this part of the work, the discussion on the influence of alcohol on gaseous and protein metabolism has been relegated to the physiology of metabolism.

The glycosuria which occasionally follows the use of alcohol is unconnected with its action as a fuel; at any rate, in the case of spirits it must be referred to the alcohol itself independently of any concomitant ingestion of large amounts of carbohydrate (84, 85).

It is observed apart from inebriety. We must distinguish from this form the alimentary glycosuria (87), which is the sequel of intoxication, and is specially connected with the ingestion of starch as well as of grape-sugar.

There is no change in the CO_2 in the blood in cats (88), or, at most, only a slight temporary rise (? retention); in rabbits, a similar result occurs when the intoxication lasts from two to two and a half hours. After longer periods there is a marked fall in the CO_2. The cause is acidosis. A marked diminution of alkalinity has been shown by titration, presumably due to volatile fatty acids.

Severe metabolic disturbances are no doubt produced by chronic alcoholism, but the existence of a direct action on the cells is shown by the occurrence of profound anatomical changes. We cannot at present define these metabolic disturbances further. Obviously, a clear line must be drawn between the chronic alcoholism of the beer-drinker, in which there is frequently overnutrition, and the simpler form following on the abuse of wine and spirits. Many recent proofs have been adduced

as to the fatty changes in the organs (89). The percentage of fat in the liver and heart of starved dogs a few days after the ingestion of alcohol is increased when compared with the controls. In the liver the amount certainly rises above the normal in starvation. The fatty liver does not occur when sugar is taken after the alcohol. No fatty change was noted after two days of alcohol ingestion. This is remarkable, considering the opposite result which followed a single dose of chloroform.

Very accurate estimations have been made of the alkalinity of the blood in experiments on chronic alcoholism in rabbits. Except during absolute drunkenness, the amount of CO_2 in the blood remains unaltered, even after several weeks of alcohol. This is also true of cats. The oxygen content is decreased (*vide infra*).

On the other hand, after alcohol had been given for a month—even apart from intoxication—there was a diminution of CO_2 in the blood. This has also been shown to occur in man (90). But no observer has found any diminution of alkalinity by titration. Hence the decrease in CO_2 must depend on diminished production, or on an abnormally active ventilation of the blood. Against the occurrence of the latter alternative is the fact that the O_2 content of the blood is not merely *not* raised, but is abnormally low. There is, no doubt, as a rule, a diminution of the number of erythrocytes in the course of chronic alcoholism, whereby the oxidative capacity of the cells is damaged, but no certain cause can be assigned for the diminution of the CO_2.

Experiments on the alimentary glycosuria of spirit-drinkers have shown that this is only recognisable during the first three days—in one case during the first week—after the end of the intoxication. Later than this it occurs no more easily than in healthy men. Thus chronic alcoholism, unlike some disorders in this respect, has no specific action on carbohydrate metabolism. The feeding with carbohydrates for long periods makes no difference. The use of alcohol usually appears to exert no specific influence on the production or the course of diabetes.

Salant (101) could not find that alcohol exercised any sparing effect on the hepatic glycogen, and large amounts seemed to hasten its disappearance, but only after the stage of intoxication was passed. The doses given were high—12 to 15 c.c. 60 per cent. alcohol per kilogramme in some cases.

LITERATURE.

1. Rumpf: Über die Wärmregulation in der Narkose und im Schlaf. Ar. P. M. 33. 538. 1881.

2. Richet: De l'infl. du chloral sur les actions chim. respirat. chez le chien. Trav. d. lab. d. Richet. 1. 431. 1893.

3. Quinquaud: Sur l'action de la Paraldehyde. C. r. S. B. 1884. 142. 215.

4. von Böck u. Bauer: Ueber den Einfl. einiger Arzneimittel auf den Gasaustausch bei Tieren. Z. B. 10. 363. 1874.

5. Binz: Ueber die antipyret. Wirk. von Chinin und Alkohol. Ar. p. A. 51. 152. 1870.

6. Henrijean: Infl. des agents antitherm. sur les oxydations organiques. T. F. 1. 113. 1887.

7. Chittenden: Ueber den Einfl. von Urethan, Antipyrin und Antifebrin auf den Eiweissumsatz. Z. B. 25. 496. 1888.

8. Müller: Ü. den Einfl. von Chloralhydrat, etc., auf die Kohlensäureaussch. des tier. Organismus. Diss. Erlangen, 1891.

9. Bert: La pression barométrique. 1878.
10. Gottlieb: Theorie der Narkose. Er. Ph. I. **2.** 666. 1902.
11. Loewi: Pharmak. des Wärmehaushalts. Er. Ph. **3.** 1. 332. 1904.
12. Friedländer u. Herter: Ueber die Wirk. der Kohlensaure auf den tier. Organismus. Z. p. C. **2.** 99. 1878.
13. Kunkel: Handb. der Toxikologie. Jena, 1899.
14. von Nencki u. Sieber: Ueber eine neue Methode, die physiol. Oxydation zu messen und über den Einfl. der Gifte und Krankh. auf dieselbe. Ar. P. M. **31.** 319. 1883.
15. Simanowsky u. Schoumoff: Ueber den Einfl. des Alkohols und des Morphiums auf die tier. Oxydation. Ar. P. M. **33.** 251. 1884.
16. Loewi: Pharmak. des Wärmehaushalts. Er. Ph. III. **1.** 332. 1904.
17. Nebelthau: Zur Glykogenbild. in der Leber. Z. B. **28.** 138. 1891.
18. Lépine et Porteret: De l'infl. qu'exercent les subst. antipyrét. et en partic. sur la teneur du foie en glycogène. C. r. A. S.. **106.** 1023. 1888.
19. Rosenbaum: Ueber den Kohlehydratbestand des tier. Organismus nach Vergift. mit Arsen, etc. Diss. Dorpat, 1879.
20. Eckhardt: Ueber den Einfl. des Chloralhydrats auf gewisse exper. zu erzeugende Diabetesformen. E. A. **12.** 275. 1880.
21. Kaufmann: Ueber die Einwirk. von Medikamenten auf die Glykosurie der Diabetiker. Z. M. **48.** 260, 436. 1903.
22. Loewy: Ueber den Einfl. einiger Schlafmittel auf die Erregbarkeit des Atemzentrums nebst einigen Beobacht. über die Intensität des Gaswech. im Schlaf des Menschen. B. k. W. **1891.** 434.
23. Richter: Zur Kennt. der Wirkungsweise gewisser die Zuckeraussch. herabsetzender Mittel. Z. M. **36.** 152. 1898.
24. Dreser: Ueber die Wirk. einiger Derivate des Morphins auf die Atmung. Ar. P. M. **72.** 485. 1898.
25. Impens: Ueber die Wirk. des Morphins und seiner Derivate auf die Atmung. Ibid. **78.** 527. 1899.
26. Scheinesson: Über den Einfl. des Chloroforms auf die Wärmeverhält. des tier. Organismus und den Blutkreislauf. Diss. Dorpat, 1865.
27. Vas: Zur Kennt. der chron. Nikotin- und Alkoholvergiftung. E. A. **33.** 140. 1894.
28. Gottlieb: Die Theorie der Narkose. Er. Ph. **1.** 2. 666. 1902.
29. Jaquet: Der respirat. Gaswechsel. Er. Ph. **2.** 2. 457. 1903.
30. Strassmann: Die tödliche Nachwirk. des Chloroforms. Ar. p. A. **115.** 1. 1889.
31. Ken Taniguti: Ueber den Einfl. einiger Narcotica auf den Eiweisszerfall. Ar. p. A. **120.** 21. 1890.
32. Salkowski: Zur Kennt. der Wirkungen des Chloroforms. Ar. p. A. **115.** 339. 1889.
33. Rostoski: Ueber die Steigerung des Eiweisszerfalls durch Protoplasmagifte, speziell Chloroform, bei Pflanzenfressern. Z. p. C. **31.** 432. 1901.
34. Sawelieff: Ueber den Einfl. des Eiweisszerfalls auf die Aussch. des neutralen Schwefels. Ar. p. A. **136.** 195. 1894.
35. Benedikt: Ueber die Aussch. des Schwefels in pathol. Zuständen. Z. M. **36.** 251. 1898.
36. Peiser: Ueber den Einfl. des Amylenhyd. and Chloralhyd. auf die N-Aussch. beim Menschen. F. M. **11.** 1. 1893.
37. Harnack u. Remertz: Ueber die Beeinflus. der Schwefel- und Stickstoffaussch. durch das Chloralhyd. und Amylenhydrat. F. M. **11.** 7. 1893.
38. Harnack u. Kleine: Ueber den Wert genauer Schwefelbestim. im Harn für die Beurteil. von Veränderungen des Stoffwech. Z. B. **37.** 417. 1899.
39. Gordon: A Contrib. of the Study of Chloralamide. B. M. J. **1891.** 1060.
40. Harnack: Über Chloral- und Amylenhydrat. Mü. m. W. **1893.** 610.
41. Kast: Ueber Beziehungen der Chloraussch. zum Gesamtstoffwechsel. Z. p. C. **12.** 267. 1888.
42. Ostertag: Die tödl. Nachwirkung des Chloroforms. Ar. p. A. **118.** 250. 1889.
43. Rosenfeld: Studien über Organverfettungen. E. A. **55.** 179. 1906.
44. Kast u. Mester: Ueber Stoffwechselstör. nach länger dauernden Chloroformnarkosen. Z. M. **18.** 468. 1891.

45. Schmidt: Ueber Veränderungen der Herzganglien durch Chloroformnarkosen. Z. B. **37.** 43. 1899.

46. Ungar: Ueber tödl. Nachwirk. der Chloroforminhal. Vierteljahrs. f. ger. M. **47.** 98. 1886.

47. Gading: Ueber die Ursachen und Leichenerscheinungen des Chloroformtodes. Diss. Berlin, 1879.

48. Lengemann: Sind die schädl. Nachwirk. des Chloroforms von der Tech. der Narkose abhängig. Be. C. **27.** 805. 1900.

49. Nothnagel: Die fettige Degen. der Organe bei Aether- und Chloroformvergift. B. k. W. **1866.** 32.

50. Salkowski: Ueber die Entsteh. der Schwefelsäure und das Verhalt. des Taurins im Tierkörper. Ar. p. A. **58.** 460. 1873.

51. Lépine, Guérin, Flavard: Ein neues Symptom der Gallenaussch. Rc. m. **1.** 27 and 911. 1881.

52. Stadthagen: Zur Kenntnis der Zystinurie. Ar. p. A. **100.** 416. 1885.

53. Jawein: Über den Einfl. des Natriumkarbonats resp. -Zitrats in grossen Dosen gegeben auf den N-Umsatz. Z. M. **22.** 43. 1893.

54. Heffter: Die Aussch. des Schwefels im Harn. Ar. P. M. **38.** 476. 1886.

55. Harnack: Ueber den sog. peptonartigen Körper im Hundeharn. B. k. W. **1893.** 1138.

56. Levinstein: Zur Path. der akuten Morphium- und Chloralvergift. B. k. W. **1876.** 27.

57. Manchot: Ueber Melliturie nach Chloralamid. Ar. p. A. **136.** 368. 1894.

58. Heinsberg: Ueber die Einwirk. der $CHCl_3$-Narkose auf den Kohlehydratbestand. Diss. Würzb., 1895.

59. Musculus et Mering: Ein neuer Körper im Chloralharn. Mem. Soc. Med. de Strasb. **12.** 106. 1876.

60. Peiper: Alkalimet. Unters. des Blutes unter norm. und pathol. Zuständen. Ar. p. A. **116.** 337. 1889.

61. Behring: Die Blutserumther. und die Immunisierungsmeth. 1892.—Beitr. zur Aetiol. des Milzbrandes. Z. Hy. **6.** 117, 467. 1889.

62. Kraus: Ueber die Alkaleszenz des Blutes und ihre Aenderung durch Zerfall der roten Blutkörperchen. E. A. **26.** 186. 1890.

63. Harnack u. Meyer: Das Amylenhydrat. Z. M. **24.** 374. 1894.

64. Schaumann: Ueber den Einfl. des Sulfonals und Trionals auf den menschl. Stoffw. T. M. **8.** 383. 1894.

65. Hahn: Ueber den Einfl. des Sulfonals auf den Eiweisszerfall. Ar. p. A. **125.** 182. 1891.

66. Smith: Ueber das physiol. Verhalten des Sulfonals. T. M. **2.** 507. 1888.

67. Chittenden: Ueber den Einfl. von Urethan, etc., auf den Eiweissumsatz. Z. B. **25.** 513. 1888.

68. Trautmann: Der Einfl. des Veronals auf die Stickstoffaussch. beim Menschen. T. G. **1903.**

69. Rudenko: Ueber das Verhalt. des neutralen Schwefels bei Stoffwechselveränd. und ü. die Oxyd. desselben im tier. Organismus. Ar. p. A. **125.** 102. 1891.

70. Thomas: Ueber die Wirk. einiger narkot. Mittel auf die Blutgase, die Blutalkal. und die roten Blutkörperchen. E. A. **41.** 1. 1898.

71. Rubow: Ueber den Lezithingeh. des Herzens und der Nieren unter norm. Verhältnissen, im Hungerzustand und bei der fett. Degeneration. E. A. **52.** 173. 1904.

72. Naunyn: Der Diab. mellitus. 1898.

73. Kast u. Weiss: Zur Kenntnis der Hämatoporph. B. k. W. **1896.** 621.

74. Quincke: Sulfonalvergift. im Harn. B. k. W. **1892.** 889.

75. Stokvis: Zur Pathogen. der Hämatoporphyrinurie. Z. M. **28.** 1. 1895.

76. Neubauer: Hämatoporph. und Sulfonalvergift. E. A. **43.** 456. 1900.

77. Schulz: Ueber einige Farbst. des Harns. Er. Ph. II. **1.** 159. 1903.

78. Garrod and Hopkins: On the Occurrence of Hæmatoporphyrine in Urine of Patients taking Sulphonal. J. P. and B. **1896.** 434.

79. Nasse: Ueber prim. und sekundäre Oxydation. Ar. P. M. **41.** 378. 1887.

80. Bendix: Ueber aliment. Glykosurie nach Narkosen. C. S. **3.** 149. 1902.

81. Böck: Über die Zersetz. des Eiweisses unter dem Einfl. von Morphin, Chinin und arseniger Säure. Z. B. **7.** 418. 1871.

82. Luzzatto: Ueber die Natur und die Ursachen der Morphinglykosurie. E. A. **52.** 95. 1905.

83. Levinstein: Die Morphiumsucht. 1877.
84. Kratschmer: Zur Frage der Glykosurie. C. m. W. **1886.** 257.
85. Krehl: Aliment. Glykosurie nach Biergenuss. C. i. M. **1897.** 1033.
86. Hoppe-Seyler: Zur Pathol. der vorübergehenden Glykosurien. K. i. M. **1902.** 384.
87. Strauss: Über alimentäre, "spontane," und diabet. Glykosurien, etc. Z. M. **39.** 1900.
88. Meyer: Über die Alkaleszenz des Blutes. E. A. **17.** 304. 1883.
89. Rosenfeld: Über Organverfettungen. E. A. **56.** 179. 1906.
90. Kraus: Ueber die Alkaleszenz des Blutes bei Krankheiten. Z. H. **10.** 106. 1889.
91. Becker: Die Gefahren der Narkose für den Diabetiker. D. m. W. **1894.** 359. 380. 404.
92. Greven: Ueber Azetonurie nach der Narkose. Diss. Bonn. 1895.
93. Abram: Acetonuria and General Anæsthesia. J. P. and B. **3.** 430. **1896.**
94. Guthrie: Lancet, January 27, 1894.
95. Stiles and Mcdonald: Rep. Soc. Study Disease Child., vol. iv., p. 208. 1904.
96. Hubbard: B. M. & S. J., June 29, 1905; Lancet, July 22, 1905.
97. Brackett, Stone, and Low: B. M. & S. J., July 7, 1904; Lancet, 1904, ii., p. 846.
98. Beesly: B. M. J., 1906, vol. i., p. 1142.
99. Telford and Falconer: Lancet, 1906, vol. ii., p. 1341.
100. Dixon, W. E.: Manual of Pharmacology, 1906, p. 59.
101. Salant: J. Am. Med. Assoc., xlvii., p. 1467. 1906.

VII.—ANTIPYRIN.

Experiments on the respiratory interchange in man and in rabbits show no alteration, but only a general fall in gaseous metabolism (1 to 5). The trustworthy figures of Liepert and Riethus may be tabulated as follows (2 to 3 grammes antipyrin):

Case.	*Without Antipyrin.*				*With Antipyrin.*		
	O_2.[1]	CO_2.[1]	Respiratory Quotient.		O_2.	CO_2.	Respiratory Quotient.
Subject K. ..	4·1	3·4	0·83		3·7	2·6	0·70
	4·4	3·2	0·73		4·2	2·8	0·67
	4·4	3·2	0·73		4·2	2·9	0·69
Average ..	4·3	3·3	0·76		4·0	2·8	0·69
				Decrease ..	7 %	15 %	9 %
Subject G. ..	3·7	2·9	0·78		3·8	2·9	0·76
	3·7	2·9	0·78		3·4	2·7	0·78
Average ..	3·7	2·9	0·78		3·6	2·8	0·77
				Decrease ..	3 %	4 %	2 %
Subject R. ..	3·6	2·9	0·81		—	—	—
	3·7	3·0	0·81		3·6	2·7	0·75
	3·8	3·0	0·79		3·6	2·5	0·70
Average ..	3·7	3·0	0·80		3·6	2·6	0·73
				Decrease ..	3 %	13 %	10 %

[1] Calculated in c.c. per kilogramme per minute.

In a case of erysipelas similar results were obtained.

Without Antipyrin.				*With Antipyrin.*		
O_2.	CO_2.	Respiratory Quotient.		O_2.	CO_2.	Respiratory Quotient.
5·0	3·9	0·79		4·4	3·2	0·73
			Decrease ..	15 %	18 %	8 %

The temperature in these experiments remained unaltered.

Although these experiments do not point to any increased heat formation, calorimetric researches on rabbits at medium external temperatures show that there is a marked increase, calculated by comparison of the directly estimated heat loss and the body temperature, which takes place whether the body temperature remains unchanged or falls slightly (7 to 10). In guinea-pigs the heat production remained generally unchanged, but with a tendency towards a slight decrease.

Riethus's results in man are as follows :

Disease.	*Without Antipyrin.*			*With Antipyrin.*		
	O_2.	CO_2.	Respiratory Quotient.	O_2.	CO_2.	Respiratory Quotient.
Erysipelas	6·2	4·2	0·67	6·0–3	3·8–10	0·61
Polyarthritis ..	6·0	4·1	0·70	5·6–7	3·6–10	0·64
Tuberculosis (1) ..	6·1	5·1	0·83	6·5–7	5·0–2	0·77
,, (2) ..	4·7	3·8	0·81	4·1–9	3·4–10	0·83
,, (3) ..	4·8	3·4	0·71	3·6–15	2·4–30	0·86[1]
,, (4) ..	5·3	4·1	0·77	5·1–4	3·9–5	0·76
,, (5) ..	7·3	4·5	0·71	5·8–8	4·0–10	0·69

Similar results have been obtained in rabbits with pyrexia.

Calorimetric observations on dogs and rabbits whose temperature had been raised by puncture of the brain showed regularly an increased heat production (11). Infected rabbits and guinea-pigs did not give such clear results, as, owing to the continued fever, the heat production rose, or sometimes remained constant, or sank. The latter usually occurs in guinea-pigs.

Experiments on the respiratory interchange in man under the influence of antipyrin show sometimes a transient fall in the oxygen intake (3 to 15 per cent.), and a much greater CO_2 output (2 to 30 per cent.) in normal men, and in those with pyrexia. Calorimetric experiments show an increased heat production in rabbits after puncture of the corpus striatum, and usually after infection.

The question then arises as to why the CO_2 output in man is so much

[1] Symptoms of poisoning.

more increased than the oxygen intake. This cannot be determined with certainty, but apparently the antipyrin damages the respiratory mechanism. Decreased respiratory activity causes diminished CO_2 excretion, owing to the impaired ventilation of the blood. The following table from Liepelt's experiments shows how antipyrin affects the respiration :

Case.	*Without Antipyrin.*		*With Antipyrin.*		
	Frequency.	Amount per Minute.	Frequency.	Amount per Minute.	Decrease.
		c.c.		c.c.	Per Cent.
Subject K. ..	18	6,023	16·5	5,302–7,218	17
Subject G. ..	13	5,881	14·0	5,632–1,497	4
Subject R. ..	19	5,331	18·0	4,692–6,398	12

A further question crops up regarding the want of agreement between the respiration experiments on man and the calorimetric experiments on rabbits. Whereas in the first case the heat production is unchanged, or slightly decreased, it is, in the majority of the experiments, found to be increased in the latter. The determination of this point is connected with the cause of the fall in gaseous interchange in the one case and the increased heat formation in the other.

The decreased gaseous interchange in man may be due to—

1. A primary inhibitory action on metabolism similar to that of quinine.

2. A thermotaxic action, due to some power of decreasing heat production.

3. The narcotic action, with consequent decrease in functional activity.

1. This is excluded by the results of animal experiments. In dogs and rabbits, if the cord is cut high up to hinder heat loss (12, 13), or even without this (14), a rise of temperature is not reduced by antipyrin as it is by quinine. Thus, to a certain extent, a direct action of antipyrin on metabolism is disproved.

2. In the collected calorimetric observations the heat loss is regularly increased, whatever may be the behaviour of the temperature or heat production. One cause at least is the dilatation of the cutaneous vessels produced by antipyrin (15 to 18). Interference with the thermotaxic centre would produce an increase, and not a slight decrease, of heat production.

3. After 2·3 grammes of antipyrin, weariness, lassitude, and a desire for sleep are observed—symptoms of its narcotic action. The influence on respiration corresponds to this. We may compare the diminution in oxidation here noted with that following on decreased ventilation.

There are various different quantitative estimations of the influence on decreased oxygen intake and CO_2 output, as is shown in the table on p. 1160.

An increased ventilation of 1,000 c.c. per minute shows an increase of—

Author.	O_2.	CO_2.
	c.c.	c.c.
Speck (19)	10	25 (seldom more).
Loewy (20)	3–7 10–15	— —
Zuntz and Schumburg ..	7·16 7·22	— —

These figures show, as Loewy has already noted, that increased respiration influences the oxygen intake very variously in different persons. The smallest increase was about 2 c.c. We may compare Liepelt's figures. With a decrease of about 721 c.c., 149 c.c., and 639 c.c. in the lung ventilation, the oxygen intake fell from 2·3 to 4·0, from 3·7 to 3·6, and from 3·7 to 3·6 c.c. respectively.

From this comparison we see that decreased lung ventilation may cause a much greater fall in oxygen intake than Liepelt observed.

The question then arises, Why does not the decreased oxygen intake correspond to the impaired ventilation ? The cause, apparently, lies in the fact that in consequence of the primary increase in heat loss noted above, an increase in heat production (oxygen intake) regularly occurs, whereby the decrease produced by the impaired respiration is partly, or totally, concealed. The slight change in the oxygen consumption in man is made up of the two following factors :

1. Decrease, due to decreased ventilation.

2. Increase, due to compensation for the increased heat loss through the regulatory centres.

On this assumption the marked variations in the figures are easily understood. At first they depend on individual differences in the degree to which the respiratory volume is changed, and on individual differences in the oxygen consumption, and later on the condition of the regulatory centre. The fact that this centre is comparatively easily paralyzed by antipyrin in fever is easily explained by the relatively large decrease in oxygen consumption which takes place. The increased heat loss is thus easily compensated by increased heat production.

We can now explain the remarkable contrast in the figures for heat production obtained from men and rabbits. Rabbits do not usually react to antipyrin by a decreased, but by an increased, lung ventilation, as is seen by the marked increase in the amount of water evaporated ; so that in these animals there is only the thermotaxic increase of heat production as a result of the primary increase of heat loss, which later is accentuated by the increased production due to raised respiratory activity.

A.—PROTEIN METABOLISM.

1. In Health.

Some observers on man report marked variations, even in health (23, 26, 29). More reliable experiments (24, 25, 28) show that the protein metabolism is practically unchanged. Chittenden (27) estimated that about 9 per cent. less nitrogen was excreted after 2 to 4 grammes of antipyrin. The cause of this was probably decreased absorption of food. The nitrogen-content of the fæces was unaltered.

No change was noted in a dog in nitrogenous equilibrium, even after considerable doses (58 grammes in a fortnight) (30, 31).

2. In Disease.

The results in pyrexia are different, as in this case there is regularly a marked nitrogen retention (32). Müller obtained the following figures :

Typhoid, Fourth Week.

	Mean Temperature, Centigrade.							
	39·35°.	37·80°.	39·27°.	39·59°.	38·22°.	38·51°.	39·15°.	39·52°.
	2nd Day.	3rd Day.	4th Day.	5th Day.	6th Day.	7th Day.	8th Day.	9th Day.
Nitrogen in urine	19·64	11·86	19·66	23·42	17·29	17·09	22·17	22·0
Antipyrin ..	—	7 gm.	—	—	6 gm.	5 gm.	—	—

Other experiments showed a decrease in nitrogen excretion of 16 to 25 per cent. and 15 to 30 per cent., analyses of the fæces showing no impairment of absorption. As in health there is no change in protein metabolism, any specific effect on the part of antipyrin may be excluded.

What, then, is the reason of the decreased nitrogen excretion under antipyrin in pyrexia ? Here there is greatly increased protein destruction (often 50 to 100 per cent.), only a slight amount of which may be attributed to the rise in temperature, as it occurs in puncture of the brain (33, 34) and simple physical heating (35, 36). The greater portion, however, is toxic in origin, and this part—from what we know of the action of antipyrin—is uninfluenced. We must therefore conclude that the effect of antipyrin on the metabolism of nitrogen in fever is due to its antipyretic action.[1]

[1] This view is confirmed by a comparison of the effect of antipyrin on the protein metabolism in puncture of the brain and in animals suffering from an infectious fever.

B.—CARBOHYDRATE METABOLISM.

Just as in the case of narcotics, the liver is found to be very rich in glycogen, owing to the inhibitory action of antipyrin on the glycogenic function (37 to 39). No inhibitory action on the various forms of glycosuria—*e.g.*, caffeine—has been definitely established.

C.—COMPOSITION OF THE URINE.

In Chittenden's experiments on healthy men the excretion of urine was markedly diminished—in the first period by 6 per cent., and in the second by 18 per cent. In experiments on dogs it was markedly raised, the phosphoric acid, chlorine, and sulphuric acid excretion being practically unchanged.

VIII.—ANTIFEBRIN, THALLIN, KAIRIN.

A.—ANTIFEBRIN.

In healthy men, therapeutic doses do not affect protein metabolism, and dogs can take 2 to 3 grammes without showing any change. Very toxic doses (4 to 5 grammes) cause a marked increase of protein decomposition—from 30·8 to 35·7 per cent. In fever patients there is only a slight tendency to decrease.

In Chittenden's experiments on man there was a remarkable increase in urea excretion—once 10, and in another case 20 per cent. There was no marked change in the sulphuric or phosphoric acids or the chlorides.

B.—THALLIN.

In therapeutic doses the CO_2 excretion is diminished (39, 40). In small doses in man thallin also decreases the protein metabolism, though large doses in dogs produced an increased metabolism of protein (6·6 to 25·8 per cent.).

C.—KAIRIN.

The heat production in rabbits with pyrexia increased in one experiment 7 per cent. after 0·2 gramme. A calorimetric experiment on a dog also showed an increase in heat production. In man the CO_2 excretion has been found to be decreased (2), and in rabbits the oxygen intake is lowered.

LITERATURE.

1. Livierato: Verhalten des Stoffw. unter dem Einfl. versch. antipyret. Substanzen. Ma. **1885.** 406.
2. Maragliano: Ueber das Kairin. C. m. W. **22.** 673. 696. 1884.
3. Liepelt: Ueber den Einfl. von Chinin und Antipyrin auf den Gaswechsel. E. A. **43.** 151. 1899.
4. Henrijean: Infl. des agents antitherm. sur les oxydations organiques. T. F. **1.** 113. 1887.
5. Chittenden and Cummins: Influence of Some Organic and Inorganic Substances on Gas Metab. Tr. Connect. Acad. 1886, vii., abstr. in Ma. **17.** 342. 1887.
6. Riethus: Über den Gaswech. kranker Menschen und den Einfl. antipyret. Medikamente auf denselben. E. A. **44.** 240. 1900.
7. Gottlieb: Kalorimet. Unters. ü. die Wirk. des Chinins und Antipyrins. E. A. **28.** 167. 1891.
8. Stühlinger: Ueber die Einwirk. einiger antipyret. Mittel auf den Wärmehaushalt gesunder und kranker Tiere. E. A. **43.** 167. 1899.
9. Evans: The Antipyretic Action of Antifebrin. Th. G. **11.** 237. 1887.
10. Richter: Über Antipyrese und Pyrese. Ar. p. A. **123.** 118. 1891.
11. Hildebrandt: Der physiol. Wirk. der hydrolyt. Fermente. Ar. p. A. **121.** 1. 1890.
12. Sawadowski: Über die Lokalisation der wärmeregulierenden Zentren und über die Wirk. des Antipyrins. C. m. W. **1888.** 8. 9. 10.
13. Girard: De l'action de l'antipyrine sur l'un des centres termiques encéphales. Rev. méd. de Suisse rom. **1887.** 12.
14. Krehl u. Matthes, cit. by Stühlinger (8), p. 187.
15. Geigel: Die Hauttemperatur im Fieber. Verh. d. Würzb. Ges. **22.** 1.
16. Rosenthal: Thermoelek. Unters. über die Temperaturverteil. im Fieber. D. A. Suppl. **1893.** 217.
17. Kraus: Vasomotoren und Fieber. W. k. W. **1894.** 229.
18. Maragliano: Das Verhalten der Blutgefässe bei Antipyrese und im Fieber. Z. M. **14.** 309. 1888. **17.** 291. 1890.
19. Speck: Physiol. des Menschl. Atmens. **1892.** 13.
20. Loewy: Ueber einige Umstände, welche den Stoffw. bei Muskelarbeit beeinflussen. D. A. **1891.**
21. Zuntz u. Schumburg: Physiol. des Marsches. **1901.** 230.
22. Loewi: Pharmak. des Wärmehaushalts. Er. Ph. **3.** 2. 332. 1904.
23. Livierato: l. c. (Nr. 1).
24. Müller: Über Antipyrin. C. k. M. **1884.** 36.
25. Engel: Ueber die antifebrile und antizymot. Wirkung des Antipyrins. Mit. W. **2.** 93. 1886.
26. Umbach: Ueber den Einfl. des Antipyrins auf die N-Aussch. E. A. **21.** 161. 1886.
27. Chittenden: Ueber den Einfl. von Antipyrin, Urethan und Antifebrin auf den Eiweissumsatz. Z. B. **25.** 496. 1888.
28. Tausz u. Vas: Ueber den Einfl. einiger Antipyret. auf den Stoffwechsel. U. A. M. **1.** 204. 1892.
29. Jacubowitsch: Wirk. des Antipyrins auf Temper. und Stoffw. der fiebernden und gesunden Kinder. Ja. K. **13.** 372. 1885.
30. Coppola: Sull' azione fisiol. dell' antipirina. Ann. di chim. med. farm. **4.** 1. 33. 1885.
31. Kumagawa: Ueber die Wirk. einiger antipyret. Mittel auf den Eiweissumsatz im Organismus. Ar. p. A. **113.** 134. 394. 1888.
32. Riess: Ueber Stickstoffaussch. bei antipyret. Fieberbehandl. E. A. **23.** 127. 1887.
33. Schultze: Ueber den Wärmehaushalt des Kaninchens nach dem Wärmestich. E. A. **13.** 193. 1899.
34. Rolly: Über Wärmestichhyperthermie und Fieber, etc. D. Ar. M. **78.** 250. 1903.
35. Richter: Zur Kenntnis der Wirkungsweise gewisser die Zuckeraussch. herabsetzender Mittel. Z. M. **36.** 152. 1898.

36. Linser u. Schmid: Ueber den Stoffw. bei Hyperthermie. D. Ar. M. **79.** 514. 1904.
37. Lépine et Porteret: De l'infl. qu'exercent les substances antipyrét. et en particulier sur la teneur, etc. C. r. A. S. **106.** 1023. 1887.
38. Nebelthau: Zur Glykogenbild. in der Leber. Z. B. **28.** 138. 1891.
39. Livierato: Verhalten des Stoffw. unter dem Einfl. versch. antipyret. Substanzen. Ann. di chim. e di farm. 3. 322. 1885.
40. Maragliano: Über die biolog. und therap. Wirk. des Thallin. Z. M. **10.** 402. 1886.

IX.—QUININE.

Although numerous experiments have shown that quinine exercises a powerful influence on the metabolism of albumin, on the other hand they have indicated that the total metabolism is but little affected. But the results in these cases have not been quite convincing. The cause lies in the varying individual reactions to quinine both in healthy and sick persons. In the latter the temperature is often unaltered, or only to a slight degree; in the former quinine has a secondary influence on respiration, muscular tone, etc., which is liable to very marked individual variations. As the latter functions are performed at the expense of non-nitrogenous material, it is clear that the exchange of carbohydrate and fat will show greater variations than that of albumin.

A.—EXPERIMENTS IN HEALTH.

One gramme of quinine is said to have caused a temporary decrease in CO_2 excretion in two cases (1, 2), but there are marked variations normally. Very exact observations showed in one case a slight increase in CO_2 output, and a still slighter increase in O_2 intake, one hour after the ingestion of 2 grammes of quinine sulphate (3 to 5). This was attributed to the by-effects of quinine—*e.g.*, increase in the volume of respiration, shivering, etc. Zuntz's table is appended:

Respiration calculated during One Minute (Average Figures).

Volume of Respiration.	*Oxygen Intake.*	*CO_2 Output.*	*Respiratory Quotient.*	*Period.*	*Remarks.*
3,935	171·4	140·8	0·82	Before quinine.	Fasting.
4,973	186·0	149·4	0·79	With ,,	,,
4,228	184·4	146·8	0·80	After ,,	,,
6,420	229·6	202·1	0·88	Before ,,	After breakfast.
5,214	233·5	197·6	0·85	With ,,	,, ,,
5,759	249·7	205·7	0·83	After ,,	,, dinner.
6,183	247·1	208·5	0·84	With ,,	,, ,,

As the volume of respiration, the oxygen intake, and CO_2 output were only increased in the fasting condition, we may conclude with Zuntz that there is no specific action independent of concomitant circumstances.

Liepelt's figures are similar :

Calculated per Kilogramme per Minute.

Subject.	*Without Quinine.*		*With Quinine.*		*Dose.*
	O_2.	CO_2.	O_2.	CO_2.	
					Gm.
K. ..	4·1	3·4	4·4	3·0	1·0
	4·4	3·2	4·6	3·3	1·5
	4·4	3·3	—	—	—
G. ..	3·7	2·9	4·4	3·6	1·0
	3·7	2·9	4·3	2·6	1·5
R. ..	3·6	2·9	4·1	3·3	1·0
	3·7	3·0	4·0	3·2	1·0
	3·8	3·0	—	—	—

Here there is regularly a slight rise in the intake of oxygen and an occasional rise in CO_2 output, which we may refer with Liepelt to the by-effect of the quinine.

The gaseous metabolism in rabbits was unchanged in most experiments (6 to 8), though Chittenden and Cummins (9) found a slight decrease in rabbits, and Böck and Bauer (10) in cats. When the animals moved more actively, the last observers noted an increased excretion.

Direct calorimetric estimations on rabbits showed in one case a fall in heat loss during the first hour after subcutaneous injection, but only of that part due to radiation and conduction (11, 12). As the temperature sank at the same time, the heat production must have been decreased, unless the heat loss was correspondingly raised by evaporation. The heat loss by evaporation has also been estimated. In all cases the heat loss increased. In three instances in which the temperature remained the same the heat production increased correspondingly ; in the two others in which it fell somewhat there was also some slight increase in heat production. In an experiment in which the quinine was given by the mouth, after a slight temporary rise there was a fall in heat loss, with a slowly falling temperature. In contradiction to all the other results, the oxidation processes were below normal.

The difference between these results may be explained by the fact that in the last-quoted there was marked increase in vaporation during the first hour. Considering this, there may possibly have been an increased heat production in the first series.

B.—ACTION IN PYREXIA.

In erysipelas and other conditions a well-marked fall in CO_2 output has been observed (13, 14). This illustrates the remarkable difference between the action of quinine on healthy and feverish persons, which is illustrated by the following figures from a case of erysipelas [Riethus (14)] :

Calculated per Kilogramme per Minute.

Apyrexial Period.				*Pyrexial Period.*			
Without Quinine.		With Quinine.		Without Quinine.		With Quinine.	
O_2.	CO_2.	O_2.	CO_2.	O_2.	CO_2.	O_2.	CO_2.
5·0	3·7	5·1	3·7	7·7	4·1	7·0	4·3

In other cases of Riethus' (typhoid and pulmonary consumption) there was no distinct effect observable.

In rabbits with fever the CO_2 output always fell [Strassburg and others].

Calorimetric experiments in animals with cerebral puncture showed decreased heat production, as had been assumed from the fact that rabbits with septicæmia showed decreased heat loss and a fall of temperature under quinine [Gottlieb and Stühlinger].

Summary.

1. In health, heat production, as calculated from the gaseous exchange, is usually unchanged. Calorimetric observations show a slight rise, as both total heat loss and temperature go up. When this does not occur, the fall is not great enough to exclude oxidation processes.

2. In pyrexia, when the temperature is reduced, the majority of experiments on gaseous exchange and with the calorimeter show decreased heat production, while, at the same time, the heat loss—in man, at any rate, by radiation and conduction (15, 16)—is increased. The decrease in heat production is primary, and not due to a thermotaxic action, which would produce a contrary effect. It is the result of a direct action on the cell protoplasm, as the temperature falls in animals in which the central nervous system is destroyed and the heat loss prevented (17 to 20).

The difference in heat production in conditions of health and pyrexia is probably quantitative only, and not one of principle. In both conditions quinine most probably decreases the oxidative power, but, owing to special circumstances, this takes place more actively in pyrexia. Increased metabolism due to the motor stimulation, which is almost always observed, prevents the effects of decreased oxidation being apparent in healthy persons. This, however, is a purely hypothetical explanation.

C.—PROTEIN METABOLISM.

Many experiments on this point have been made, and a decrease has been shown to occur in healthy men of from 24 to 39 per cent. (22 to 29); in dogs, of 8 to 16 per cent., and during starvation, of 36 per cent. (30).

An increase has been reported by one observer (32), but his figures are uncertain, and show too great variations. The increase so carefully

observed by Oppenheim (33) is not in opposition to the results quoted above, as he only gave one dose of quinine, and only estimated the excretion of nitrogen during one day. An increase often occurs on the first day. The following table shows that the cause of the decreased nitrogen excretion in urine is not some impediment to nitrogen absorption, as seemed to be the case from the experiment on a starving dog. Both experiments were similar. In the first, nitrogenous equilibrium was established before quinine was given, and in the second it was not. In each case the effect of the quinine was to decrease metabolism, so that in the first there was marked nitrogen retention (0·9 gramme per diem), and in the second there was a decrease in the nitrogen deficit (0·7 gramme per diem). The action was most marked on the second day. A significant confirmation of the experiment would be obtained by determining whether the nitrogen saved was not lost little by little later on. The phosphorus curve in the urine approximates to that of the nitrogen, but is less pronounced.

Uric Acid Excretion in Grammes.

Number of Experiment.	*Before Quinine.*	*Quinine Period.*	*Period after Quinine.*	
			First Half.	Second Half.
1	0·70–0·95	0·75–0·87	0·50–0·58	0·76
2	0·59–0·65	0·68–0·45	0·39–0·44	0·64–0·68

Experiment on Himself by Dr. Irisawa, aged Twenty-eight.

Before the experiment, weight 50·9 kilogrammes.
After ,, ,, ,, 49·9 ,,

Diet: 250 grammes rice; 100 grammes sausage; 50 grammes cake; 30 grammes butter; about 130 grammes eggs; 200 grammes meat; 1,960 c.c. H_2O; 5 grammes NaCl—*i.e.*, 109 to 112 grammes albumin, 92 to 94·2 grammes fat; 240 grammes carbohydrate=2,260 to 2,280 calories, or 44 calories per kilogramme.

Day.	*Nitrogen Intake (Gm.).*	*Nitrogen Output (Gm.).*		*Nitrogen Balance (Gm.).*		*P_2O_5 in Urine (Gm.).*		*Fat in Fæces (Gm.).*	*Amount of Urine (c.c.).*	*Quinine (Gm.).*
		Urine.	Fæces.	Per Diem.	Average.	Per Diem.	Average.			
1	17·604	15·324	1·742	+0·538	—	—	—	2·890	1,330	—
2	17·924	15·126	1·742	+1·056	—	2·907	—	2·890	1,700	—
3	17·968	15·565	1·742	+0·661	—	2·669	—	2·890	1,700	—
4	17·458	14·741	1·742	+1·005	—	2·298	—	2·890	1,630	—
5	17·458	16·032	1·742	−0·316	−0·014	2·590	2·525	2·890	1,400	—
6	17·480	15·450	1·742	+0·288		2·460		2·890	1,330	—
7	17·516	16·723	1·365	−0·562	+0·903	2·686	2·449	2·534	1,580	0·5
8	17·508	15·291	1·365	+0·952		2·520		2·534	1,800	0·7
9	17·995	15·079	1·365	+1·551		2·356		2·534	1,980	1·1
10	17·955	14·918	1·365	+1·672		2·133		2·534	1,580	1·4
11	17·854	14·784	1·364	+1·706	+1·754	1·984	2·284	2·625	1,280	—
12	17·832	13·691	1·364	+2·777		2·275		2·625	1,300	—
13	17·854	14·461	1·364	+2·029		2·342		2·625	1,280	—
14	17·854	15·986	1·364	+0·504		2·534		2·625	1,440	—
15	17·853	16·576	1·364	−0·187	—	2·704	—	2·625	1,600	—

In a second experiment the amount of albumin in the diet was much decreased.

Diet: 55-56 grammes albumin; 107·6 to 108·7 grammes fat; 291·05 grammes carbohydrate=2,424 calories, or 49 calories per kilogramme.

Day.	*Nitrogen Intake (Gm.).*	*Nitrogen Output (Gm.).*		*Nitrogen Balance (Gm.).*		*P_2O_5 in Urine. (Gm.).*		*Fat in Fæces (c.c.).*	*Quinine (Gm.).*
		Urine.	Fæces.	Per Diem.	Average.	Per Diem.	Average.		
1	8·992	10·111	1·496	−2·615	—	—	—	3·280	—
2	8·992	9·571	1·496	−2·075	—	1·994	—	3·280	—
3	9·992	9·104	1·496	−1·608	—	1·609	—	3·280	—
4	9·036	8·683	1·496	−1·143		1·680		3·280	—
5	9·036	8·871	1·496	−1·331	−1·142	1·869	1·755	3·280	—
6	9·036	8·491	1·496	−0·951		1·716		3·280	—
7	9·028	9·027	1·229	−1·223		1·884		2·190	0·5
8	9·064	8·435	1·229	−0·600		1·596		2·190	0·7
9	9·136	8·058	1·229	−0·151	−0·414	1·256	1·475	2·190	1·1
10	9·137	8·344	1·229	−0·436		1·500		2·190	1·4
11	9·137	8·568	1·229	+0·342		1·139		2·190	1·4
12	9·030	7·718	1·539	−0·221		1·142		2·492	—
13	9·014	6·789	1·539	+0·686	+0·233	1·342	1·242	2·492	—
14	9·036	8·584	1·539	−1·087		1·662		2·492	—
15	9·057	8·871	1·539	−1·353	−1·220	1·663	1·663	2·492	—

The leucocyte count showed:

Number of Experiment.	*Before Quinine.*	*During Quinine.*	*After Quinine.*
1	3,800–6,700	5,440–4,650	5,800–6,700
2	5,840–6,750	5,670–4,940	5,840–6,750

In fever there is also a distinct nitrogen retention (35). Some irregularities have been observed, but no conclusions can be drawn from them (36).

The first table on p. 1167 shows the ratio of the urea nitrogen to the total nitrogen in the urine, and also the effect of long-continued use of quinine. It is taken from one of the author's unpublished observations.

The figures at the beginning of the quinine treatment show a certain decrease in the percentage of urea. It is caused by the fact that the absolute amount of residual nitrogen remains unaltered, and denotes decreased protein katabolism. The same thing was observed by Folin (37) in the conclusive and remarkable experiment given on p. 1167 (second table), in which the protein metabolism was decreased by diminishing the supply.

The absorption being normal, and as experiments by Loewy have shown that the excretion is uninfluenced by quinine, the nitrogen retention can only be attributed to the decreased katabolism of nitrogenous material, owing to the action of the quinine on cell-protoplasm.

That this is actually the case is shown by various considerations. Firstly, because, as we have seen, the temperature is reduced by quinine in animals after section of the cord, whereby increased heat loss from the skin is excluded. Secondly, certain fermentative processes are inhibited by quinine—*e.g.*, the conversion of glycogen into sugar by the inverting

Subject, Dog: Intake of 250 Grammes Meat and 40 Grammes Fat Daily.

Day.	*Nitrogen in Urine.*	*Urea in Urine.*	*Urea Nitrogen in Total Nitrogen.*	*Remarks.*
	Gm.	Gm.	Per Cent.	
1	7·87	6·27	80·0	—
2	7·89	6·13	76·0	—
3	15·95	14·0	87·5	+ 15 gm. urea.
4	8·20	7·19	87·5	—
5	7·90	6·80	86·0	—
6	7·34	6·35	87·0	0·5 gm. quinine.
7	6·67	5·46	82·0	1·0 ,,
8	6·88	5·77	84·0	1·0 ,,
9	7·19	5·60	78·0	1·0 ,,
10	13·00	11·93	87·0	+ 15 gm. urea.
11	6·65	5·96	89·0	1·0 gm. quinine.
12	7·16	—	—	1·0 ,,
13	8·40	—	—	1·0 ,,
14	7·90	—	—	1·0 ,,
15	8·49	—	—	1·0 ,,
16	9·27	—	—	1·5 ,,
17	7·95	—	—	1·5 ,,
18	8·40	—	—	1·5 ,,
19	8·40	—	—	1·5 ,,

ferment in the liver (38, 39). Thirdly, the formation of acid in the blood, both before and after coagulation (40), and the synthesis of hippuric acid in the kidneys, are decreased (40). Yeast fermentation is markedly diminished.

Schmiedeberg (42) thinks it probable that in the living body the processes of decomposition, oxidation, and synthesis occurring in the tissues

Nitrogen Excretion in Grammes.

	Nitrogen.	*Urea Nitrogen.*	*Per Cent.*	*NH_3 Nitrogen.*	*Per Cent.*	*Uric Acid Nitrogen.*	*Per Cent.*	*Creatin Nitrogen.*	*Per Cent.*	*X Nitrogen.*	*Per Cent.*
Diet rich in protein	16·8	14·70	87·5	0·49	3·0	0·18	1·1	0·58	3·6	0·85	4·9
Diet poor in protein	3·6	2·20	61·7	0·42	11·3	0·09	2·5	0·60	17·2	0·27	7·3

—which certainly depend on ferment action—are affected to a similar extent [*cf.* Laqueur (43)].

We must now inquire how the constant results on the protein metabolism can be reconciled to the varying effect on the total metabolism.

Is the metabolism of the non-nitrogenous material affected in a

different manner, or is the action the same, but in many instances concealed ? It has been shown that in many cases—*e.g.*, in pyrexia—the total metabolism may be decreased, and that in most cases in animals the temperature falls when the cord has been divided. This cannot be due to decreased oxidation of the non-nitrogenous material, as that of the nitrogenous is relatively too small to produce the fall in temperature. We shall probably be right in holding that quinine inhibits the total metabolism, but that this can only be shown in the case of protein, as that of the non-nitrogenous material is concealed by secondary actions, and may be overcompensated.

There are many causes for this compensation. In the first place, all experiments show that quinine produces increased heat loss. Normal warm-blooded animals react to heat loss by increased heat production, and the same thing takes place in animals under the influence of quinine, as the thermotaxic centre remains unaffected. Probably the shivering which frequently occurs is the outward expression of this thermotaxic process, though there is probably also a purely chemical heat production apart from that produced by muscular work. The non-nitrogenous substances are employed as material for this process. This will partly, at any rate, explain the increased heat production.

The special action of quinine on certain motor mechanisms may account for the rest—*e.g.*, the not infrequent spasms and vomiting, and the increased frequency of respiration. For all these processes non-nitrogenous material would be used up, and a primary decrease in oxidation processes might easily be concealed. Probably a much greater increase would occur if the inhibitory action of the quinine did not affect the non-nitrogenous substances. Perhaps some light could be thrown on the point by experiments on curarized animals similar to those on the action of pilocarpine (41). This explanation also applies to the fact that generally in healthy men the protein metabolism is decreased, but the total metabolism is unaltered, and to the diminution in both after section of the cord. Here the quinine could only affect the protein metabolism by a direct effect on the protoplasm itself. A corresponding amount of carbohydrate must be used to make up the deficiency of fuel, provided that the thermotaxic centre is intact. When this is put out of order by section of the cord, or by pyrexia, no increased oxidation of non-nitrogenous material occurs, and the total metabolism is decreased.

LITERATURE.

1. Buss : Ueber Wesen und Behandl. des Fiebers. 1878.
2. Livierato : Verhalten des Stoffw. unter dem. Einfl. versch. antipyret. Stoffe. Ma. **1885.** 406.
3. Speck : Physiol. des menschl. Atmens. **1892.** 40.
4. Zuntz u. von Noorden : Ueber die Einwirk. des Chinins auf den Stoffwechsel. D. A. **1894.** 203.
5. Liepelt : Ueber den Einfl. von Antipyrin und Chinin auf den Gaswech. des gesunden Menschen. E. A. **43.** 151. 1899.
6. Strassburg : Ueber die Aussch. der CO_2 nach Aufnahme von Chinin. E. A. **2.** 334. 1874.

7. Arntz: Ueber den Einfl. des Chinins auf Wärmeabgabe und Wärmeproduktion. Ar. P. M. **31.** 531. 1883.
8. Henrijean: Infl. des agents antitherm. sur les oxydatioms organ. T. F. **1.** 113. 1887.
9. Chittenden and Cummins, loc. cit.: See Nr. 5 on page 1163.
10. Böck u. Bauer: Ueber den Einfl. einiger Arzneimittel auf den Gasaustausch bei Tieren. Z. B. **10.** 336. 1874.
11. Gottlieb: Kalor. Unters. ü. die Wirkungsweise temp.-herabsetzender Mittel. E. A. **26.** 419. 1890.
12. Stühlinger: Ueber die Einwirk. einiger antipyret. Mittel. auf den Wärmehaushalt gesunder und kranker Tiere. E. A. **43.** 167. 1900.
13. Liebermeister: Ueber antipyret. Behandl. des Fiebers. Ges. Abhandlungen. (Leipzig.) **1889.** 365.
14. Riethus: Über den Gaswech. kranker Menschen und den Einfl. antipyret. Massnahmen auf denselben. E. A. **47.** 240. 1900.
15. Maragliano: Das Verhalten der Blutgefässe im Fieber und bei Antipyrese. Z. M. **14.** 309. 1888; **17.** 291. 1890.
16. Kraus: Vasomotoren und Fieber. W. k. W. **1894.** 229.
17. Lewitzky: Ueber den Einfl. des schwefelsauren Chinins auf die Temperatur. Ar. p. A. **47.** 315. 1869.
18. Naunyn u. Quincke: Ueber den Einfl. des Zentralnervensyst. auf die tier. Wärme. D. A. **1869.** 175. 527.
19. Binz: Ueber die antipyret. Wirk. von Chinin und Alkohol. Ar. p. A. **51.** 152. 1870.
20. Krehl u. Matthes, cit. by Stühlinger (12).
21. Meyer: Über die Alkaleszenz des Blutes. E. A. **17.** 304. 1883.
22. Schulte: Ueber den Einfl. des Chinins auf einen Oxydationsprozess im Blute. Diss. Bonn, 1870.
23. Kerner: Beitr. zur Kenntnis der Chininresorption. Ar. P. M. **3.** 93. **2.** 200. 1869-70.
24. Janssen: Über den Einfl. des schwefelsauren Chinins auf die Körperwärme und den N-Umsatz. Diss. Dorpat, 1872.
25. Kramsztyk: Arb. a. d. Labor. d. Warsch. med. Fak. **5.** 95. 1879.
26. Livierato: Verhalt. des Stoffwech. unter dem Einfl. versch. antipyret. Substanzen. An. c. F. **3.** 322. 1885.
27. von Noorden u. Zuntz: Ueber die Einwirk. des Chinins auf den Stoffwech. D. A. **1894.** 203.
28. Venediger: Ueber den Einfl. des Chinins auf die Stickstoffaussch. beim Menschen. Diss. Halle, 1893.
29. Prior: Ueber den Einfl. des Chinins auf den Stoffwech. des gesunden Organismus. Ar. P. M. **34.** 237. 1884.
30. Böck: Über die Zersetz. von Eiweiss unter dem Einfl. von Morphin., etc. Z. B. **7.** 418. 1871.
31. Kumagawa: Ueber die Wirk. einiger antipyret. Mittel auf den Eiweissumsatz im Organismus. Ar. p. A. **113.** 134. 1888.
32. Unruh: Ueber die Stickstoffaussch. bei fieberhaften Krankh. Ar. p. A. **48.** 227. 1869.
33. Oppenheim: Physiol. und Pathol. der Harnstoffaussch. Ar. P. M. **23.** 446. 1880.
34. Irisawa: Unpublished research, 1893. The manuscript was placed at my disposal by Von Noorden.
35. Sassetzky: Ueber den Einfl. fieberhafter Zustände und antipyret. Behandl. auf den Umsatz der stickstoffhaltigen Substanzen, etc. Ar. p. A. **94.** 485. 1883.
36. Bauer u. Künstle: Ueber den Einfl. antipyret. Mittel auf die Eiweisszersetz. bei Fiebernden. D. Ar. M. **24.** 53. 1879.
37. Folin: Approx. Compl. Analyses of Thirty Normal Urines. A. J. P. **13.** 45. 1905.
38. Cavazzani: Ueber den Mechan. der Zuckerbild. in der Leber. D. A. Suppl. **1899.** 105.
39. Pick: Ueber das glykogenspaltende Ferment der Leber. Be. P. P. **3.** 174. 1902.
40. Hoffmann: Ueber die Hippursäurebild. in der Niere. E. A. **7.** 233. 1877.
41. Buchheim: cit. by Schmiedeberg (42), p. 188.

42. Schmiedeberg: Grundr. der Pharmakologie. 1902. 188.
43. Laqueur: Ueber die Wirk. des Chinins auf Fermente mit Rücksicht auf seine Beeinflussung des Stoffw. E. A. **55.** 240. 1906.
44. Frank u. Voit: Ueber die Wirk. von Pilocarpin auf die Zersetz. im tier. Organismus. Z. B. **44.** 111. 1903.

X.—THE SALICYLIC ACID GROUP.

1. Salicylic Acids and Salicylates.

The investigations to hand on the influence of salicylic acid and its derivatives on the respiratory interchange, and the maintenance of temperature, are not sufficient to afford an explanation of their frequently well-marked antipyretic action. The results of individual experiments are not concordant. The cause is the well-known personal variation in relation to the drug. The differences arise in the various motor phenomena produced by the drug, such as restlessness, shivering, and increased rapidity of respiration, which occurs frequently, but by no means invariably. Thus, equal doses may not produce at all the same effect on metabolism.

In some cases sodium salicylate does not affect the CO_2 output (1), but in others it decreases it (2). In pyrexia the increased CO_2 output due to rigors is followed by a return to normal, but not below it. A marked fall in the oxygen intake has been found in rabbits with pyrexia (3). Normal rabbits showed no alteration. Singer's (4) figures for rabbits are :

Oxygen Intake.

Normal,	39·0	c.c. per minute;	after	0·2	gramme	aspirin,	32·6 =	−17 per cent.
,,	38·7	,,	,,	0·3	,,	,,	33·5 =	−14 ,,
,,	34·7	,,	,,	0·9[1]	,,	,,	37·8 =	+ 9 ,,

In guinea-pigs, after doses of 0·3 gramme the CO_2 output falls to about 44 per cent., and after doses of 0·25 to 0·5 gramme it rises about 50 per cent. (5). This is instructive, as showing that salicylates can produce contrary effects according to the size of the dose, as well as to the idiosyncrasy of the individual. It is clear from these experiments that in non-toxic doses salicylates (if they produce any effect) decrease metabolism.

Calorimetric observations on guinea-pigs showed, as a rule, a slight increase in temperature and heat production (6). The doses employed were 0·1 to 0·225 gramme, which also produced increase in CO_2 output (*vide supra*).

In therapeutic doses—if any action occurs—the protein metabolism is increased. This is different to the effect on the gaseous interchange (4 to 23).

Besides the urea, the uric acid excretion is much increased [Goodbody, Herter, Noël Paton, and others (24, 25)] It is remarkable that this rise

[1] Toxic symptoms occurred.

is relatively greater than that of the total nitrogen. With a total nitrogen increase of 7 per cent. the uric acid output rose 40 to 50 per cent. Increased protein katabolism is not the only cause of the increased uric acid excretion. Nor can it be referred to any "flushing-out" process, as salicylates produce a slight retention. W. E. Dixon (*op. cit.*) points out that the effect lasts too long to be due to improved elimination. It may continue for some days after a single dose. Walker Hall investigated the action of salicylic acid upon the endogenous uric acid excretion of meat-eaters and confirmed vegetarians, and observed that the uric acid output was consistently increased in both. Whether this is due to a diminished decomposition of uric acid precursors, or to a toxic action upon nuclein metabolism, is not quite clear (43). The excretion of phosphorus in urine and fæces is unaltered, which seems to negative any special influence of salicylates on nuclein katabolism.

Leucocytosis and a resultant destruction of the white corpuscles after administration of salicylic acid has often been assumed to be the cause of the increase in uric acid. The former has been observed to occur. The matter is discussed by Wiener (27).

The sulphate and phosphate excretion is increased correspondingly to that of the nitrogen. Some have found no change in the ethereal sulphates, others a slight rise.

The CO_2 in the blood is unaltered.

2. Benzoic and Gallic Acids.

Doses of 8 grammes of benzoic and gallic acids, or of sodium quinate, or 3 grammes of tannin per diem, do not influence protein or phosphorus metabolism in man. Benzoic anhydride and benzoyl alcohol, in small doses, are inactive in dogs (28), but large doses of benzoic acid or sodium benzoate have been observed to cause an increase of 20 per cent.

More experimental work has been done as to the influence of these bodies on uric acid excretion. Starting from the supposition that in the body uric acid is synthesized from urea and glycocoll, substances were investigated that would unite with glycocoll, in order to prevent its taking part in the uric acid synthesis. Weiss's observation that the use of fruit increased uric acid excretion threw a difficulty in the way of these researches (29), as he considered the quinic acid responsible, and stated that with it the same action could be obtained. Though not entirely unconfirmed (30), most observers have obtained opposite results (31 to 35). Weiss's position was also rendered untenable by the discovery that other bodies which combine with glycocoll—though they occasionally influence uric acid excretion—do not do so by virtue of any action on the glycocoll. A marked decrease in the uric acid excretion was shown to take place only on the first day after the exhibition of benzoic and gallic acids. It then gradually rose again, and when the drugs were discontinued, more than normal amounts were excreted. This seems to point to delayed excretion rather than to diminished production. This furnished an explanation of the absence of a fall in the uric acid output in the experiments of Weiss and Lewandowski.

Tannin has no action on nitrogenous metabolism or the excretion of uric acid, though in some experiments a decrease of the nitrogen and uric acid in the urine in almost equal proportion has been observed, apparently as the result of impaired absorption.

Salicylic acid, far from diminishing the uric acid excretion, markedly raises it, although it can combine with glycocoll; hence Weintraud (38) concludes that uric and hippuric acid formation are entirely separate and independent processes.

3. Phenol.

Non-toxic doses do not appear to influence metabolism. This has been shown for phenol itself (39, 40, 26), creolin (2 to 3 grammes), (41), and for ichthyol [4 to 4·5 grammes (42)].

LITERATURE.

1. Buss: Wesen und Behandl. des Fiebers. 1878.
2. Livierato: Verhalt. des Stoffwech. unter dem. Einfl. versch. antipyret. Substanzen. An. c. F. **3.** 322. 1885.
3. Henrijean: Infl. des substances antitherm. sur les oxydations organ. T. F. **1.** 113. 1886.
4. Singer: Ueber Aspirin. Ar. P. M. **84.** 527. 1901.
5. Livon: Sur l'action physiol. de l'acide salicyl. sur la resp. C. r. A. S. **90.** 321. 1880.
6. Stühlinger: Ueber die Einwirk. einiger antipyret. Mittel auf den Wärmehaushalt gesunder und kranker Tiere. E. A. **43.** 166. 1899.
7. Baumann u. Herter: Ueber die Synthese der Aetherschwefelsäuren u. das Verhalten einiger aromat. Substanzen im Tierkörper. Z. p. C. **1.** 244. 1877.
8. Salomé: Ueber den Einfl. des salizylsauren Natron auf die Stickstoff und Harnsäureaussch. beim Menschen. W. J. **1885.** 463.
9. Noël Paton: The Relationship of Urea Formation to Bile Secretion. J. A. and P. **20.** 1886.
10. Chopin: Aussch. der Harnsäure. Bu. g. t. Feb. **1889.**
11. Herter and E. A. Smith: On Excretion of Uric Acid in Health and Disease. N. Y. J. **1892.**
12. Tausz u. Vas: Ueber den Einfl. einiger Antipyret. auf den Stoffwechsel. U. A. M. **1.** 204. 1892.
13. Goodbody: The Influence of Sodium Salicylate on General Metabolism. J. P. **25.** 399. 1900.
14. Schreiber u. Waldvogel: Beitr. zur Kenntnis der Harnsäureaussch. E. A. **42.** 69. 1899.
15. Ulrici: Ueber pharmakol. Beeinflussung der Harnsäureaussch. E. A. **46.** 321. 1901.
16. Moreigne: Wirk. des Natriumsalizylates auf die Ernährung und besonders auf die Gallsekretion. C. m. W. **38.** 658. 1900.
17. Schreuder: Ueber den Einfl. der Salizylsäureverbind. auf die Zusammensetz. des Harns. Diss. Utrecht, 1888. Ma. **18.** 146. 1888.
18. Schreiber u. Zaudy: Zur Wirk. der Salizylpräp. insbesondere auf die Harnsäure und die Leukozyten. D. Ar. M. **62.** 242. 1898.
19. Bohr: Ueber den Einfl. der Salizylsäure auf die Fleischverdauung beim Hunde. Ma. **1876.** 188.
20. Wolfsohn: Ueber die Wirk. der Salizylsäure und des salizylsauren Natrons auf den Stoffwechsel. Diss. Königsb., 1876.
21. Salkowski: Ueber den Vorgang der Harnstoffbild. im Tierkörper und den Einfl. der Ammoniaksalze auf denselben. Z. p. C. **1.** 1. 1877.
22. C. Virchow: Ueber die Einwirk. des benzoësauren und des salizylsauren Natrons auf den Eiweissumsatz im Körper. Z. p. C. **6.** 78. 1881.

23. Kumagawa: Ueber die Wirk. einiger antipyret. Mittel auf den Eiweissumsatz im Organismus. Ar. p. A. **113.** 134. 1888.
24. Bohland: Ueber den Einfl. des salizylsauren Natrons auf die Bild. und Aussch. der Harnsäure. C. i. M. **17.** 70. 1896.
25. Magnus-Levy: Ueber Gicht. Z. M. **36.** 353. 1899.
26. De Jonge: Über das Verhalten des Phenols im Tierkörper. Z. p. C. **3.** 177. 1879.
27. Wiener: Die Harnsäure. Er. Ph. **1.** 555. 1902.
28. Jolin: Ueber die Einwirk. neutraler säurebildender Stoffe auf die Alkaliaussch. der Fleischfresser. Sk. Ar. P. **1.** 442. 1889.
29. Weiss: Beitr. zur Erforschung der Bedingungen der Harnsäurebild. Z. p. C. **25.** 393. 1898; **27.** 216. 1899.
30. Blumenthal u. Lewin: Ueber Sidonal. T. G. **1900.** Nr. 4.
31. Hupfer: Einwirk. von Chinasäure auf Harnsäureaussch. Z. p. C. **37.** 302. 1902.
32. Nicolaier u. Hagenberg: Ueber Chinotropin. C. S. **1.** 131. 1900.
33. De la Camp: Chinasäure und Gicht. Mü. m. W. **1901.** 1203.
34. Lewandowski: Über den Einfl. der Benzoesäure auf die Harnsäurebild. Z. M. **40.** 202. 1900.
35. Förster: Über die Beeinfluss. der Harnsäureaussch. mit spezieller Berücksichtigung der Chinasäure, etc. Diss. Breslau, 1900.
36. Levison: Ueber den Einfl. einiger Medikamente auf Harnsäureaussch. und Leukozytenzahl. Diss. Bonn, 1897.
37. Wolff: Ueber den Einfl. von nukleinreicher Nahrung und Acid. tannicum auf die Harnsäureaussch. Diss. Bonn, 1898.
38. Weintraud: Ueber den Abbau des Nukleins im Stoffwechsel. K. i. M. **1900.** 232.
39. Tauber: Beitr. zur Kenntnis über das Verhalten des Phenols im tier. Organismus. Z. p. C. **2.** 366. 1878.
40. Schaffer: Ueber die Aussch. des dem Tierkörper zugeführten Phenols. J. P. C. **18.** 282. 1878.
41. Mugdan: Ueber die Giftigkeit des Kreolins und seinen Einfl. auf den Stoffwechsel. Ar. p. A. **120.** 131. 1890.
42. Helmers: Ueber den Einfl. des Ichthyols auf den Stoffwechsel. Ar. p. A. **135.** H. 1. 1894.
43. Walker Hall: Excreta of Gouty Patients. B. M. J. 1904.

XI.—CAFFEINE.

The purin bodies in coffee and tea act variously in individual cases as stimulants to the motor centres. The ordinary doses which we take every day cannot be shown to have a direct influence on metabolism in men apart from this, as is shown by the unpublished experiments by Magnus-Levy (1) given on p. 1176.

The slight rise in the third experiment was doubtless due to collateral conditions, such as increased activity, fuller, stronger pulse, and a very warm skin.

Similar results were obtained by Speck (2). In rabbits, large doses of caffeine produce marked stimulation, as is shown by the rise in the oxygen intake and the CO_2 output (3).

Protein metabolism is likewise uninfluenced in a specific manner either in man (4) or dogs in nitrogenous equilibrium, or during starvation (5 to 7). After toxic doses a dog showed a marked increase in nitrogen excretion.

In rabbits the diuresis is often accompanied by glycosuria (8). The

cause is hyperglycæmia (9, 10). In addition to this, a specific action on the kidneys has been supposed to exist by Rose, because, though he observed hyperglycæmia as often after operative procedures as after caffeine, glycosuria was much commoner as a result of the latter.

	Normal Fasting (One Hour).	*Action of Coffee.*			
		First Hour.	Second Hour.	Third Hour.	Fourth Hour.
1. 500 c.c. coffee made from 15 grammes berries	O_2 c.c. per minute 258·200	242·300	248·900	247·000	—
	Respiratory quotient 0·864	0·814	0·847	0·804	—
	Per cent. change ..	−6	−3	−4	—
2. 640 c.c. coffee made from 20 grammes berries	O_2 c.c. per minute 257·400	264·700	260·600	266·300	—
	Respiratory quotient 0·770	0·719	0·728	0·711	—
	Per cent. change ..	+3	+1	+4	—
3. 350 c.c. coffee made from 25 grammes berries	O_2 c.c. per minute 233·800	251·500	—	247·800	259·400
	Respiratory quotient 0·725	0·744	—	0·750	0·749
	Per cent. change ..	+8	—	+6	+11

Passing changes in the excretion of other substances are due to the diuretic action of the purin bodies, and have nothing to do with their effect on metabolism (11 to 14).

LITERATURE.

1. Magnus-Levy: Briefliche Mitteilung.
2. Speck: Physiol. des Menschl. Atmens. 1892.
3. Heerlein: Das Koffein und das Kaffeedestillat in ihrer Beziehung zum Stoffwechsel. Ar. P. M. **52.** 165. 1892.
4. Voit: Über den Einfl. des Kochsalzes des Kaffees und der Muskelbewegungen auf den Stoffwechsel. 1860.
5. Krüger u. Schmid: Der Einfl. des Koffein und Theobromin auf die Aussch. der Purinkörper im Harn. Z. p. C. **32.** 104. 1901.
6. Ottolenghi u. Fubini: Einfl. des Koffeins und des Kaffeeaufgusses auf die tägl. Harnstoffaussch. beim Menschen. Gi. T. **45.** 570. 1882.
7. Ribaut: Infl. de la caféine sur l'excrétion azotée. C. r. S. B. **53.** 393. 1901.
8. Jacobi: Ueber künstl. Nierendiabetes. E. A. **35.** 213. 1895.
9. Richter: Diuretica und Glykosurie. Z. M. **35.** 463. 1898.
10. Rose: Der Blutzuckergeh. des Kaninchens, seine Erhöhung durch Aderlass, etc. E. A. **50.** 15. 1903.
11. Schröder: Ueber die Wirk. des Koffeins als Diureticum. E. A. **22.** 39. 1887.
12. Loewi: Physiol. und Pharm. der Nierenfunktion. E. A. **48.** 410. 1902.
13. Dreser: Über Theocindiurese am gesunden Menschen. B. k. W. **1903.** 953.
14. Katsuyama: Ueber den Einfl. des Thein auf die Aussch. von Alkalien im Harn. Z. p. C. **28.** 587. 1899; Ueber den Einfl. einiger harntreibender Mittel auf die Aussch. von Alkalien im Harn. Z. p. C. **32.** 235. 1901.

XII.—COCAINE.

Cocaine acts as a stimulant to the central nervous system. Experiments on its effects on metabolism, in spite of their incomplete character, point to a specific action, quite apart from its effect as a stimulant.

In dogs, both starved and in nitrogenous equilibrium, after one or more days' treatment with cocaine—in spite of distinct stimulation—a very considerable decrease in the urinary nitrogen was observed (1, 2). The simultaneous decrease in the amount of urine, though marked, was not sufficiently regular to account for the phenomenon. A considerable absolute increase in the total and the neutral sulphur, and a diminution in the power to oxidize benzol and to form phenol-sulphonates, has also been observed (3). Large doses caused the appearance of sugar and lactic acid in the urine of rabbits (4). This was attributed to decreased supply of oxygen, owing to inadequate respiration (?). Phlorizin is said to produce slight glycosuria after cocaine (? as a result of increased protein decomposition). Further experiments are needed to explain these actions of the drug.

LITERATURE.

1. Fleischer: Ueber die Einwirk. des Kokains auf das Nervensyst. und den Stoffwechsel. D. Ar. M. **42.** 82. 1888.
2. Maestro: Die Veränderungen des Reduktionsvermögens des Harns bei exper. Kokainvergift. S. **58.** 599. 1904.
3. Bonanni: Die Vorgänge der Oxydat. und Synthese bei chron. Vergift. mit salzaurem Kokain. Bu. R. **1900.** 26. Ma. **30.** 570. 1900.
4. Araki: Ueber die Bild. von Milchsäure und Glykose bei Sauerstoffmangel. Z. p. C. **15.** 548. 1891.

XIII.—PILOCARPINE.

As pilocarpine strongly stimulates glandular activity, its employment, it was supposed, would throw some light on the nature and origin of this process.

Frank and Voit (1) obtained the following figures for CO_2 output in dogs:

	Hour.								
	1.	2.	3.	4.	5.	6.	7.	8.	9.
Temperature (C.)..	38·35°	38·70°	38·92°	38·98°	39·07°	38·42°	38·74°	38·960°	39·160°
CO_2 (c.c.)	15·67	17·35	17·44	17·58	17·26	16·27	17·70	19·200	17·690
Pilocarpine (gm.)..	—	—	—	—	—	—	—	0·015	0·015
Saliva (c.c.)	—	—	—	—	—	—	—	80·000	42·000

The CO_2 output, which was originally very steady, rose considerably during the first hour after the dose of pilocarpine, but as it returned to its former value during the second hour—although the saliva secretion was very energetic—it is questionable whether the increased CO_2 output was really due to the glandular activity. It may have been a result of the augmented activity of the smooth muscle of the intestine, which has been shown to cease long before the salivary excretion diminishes.

There is only one detailed investigation connected with protein metabolism (2). At first, both in men and dogs in nitrogenous equilibrium or during starvation, no change is observed. In dogs, however, on the second, third, or fourth day a most remarkable rise in excretion occurs. For example :

Experiment on a Starved Dog.

Day.	*Urine.*	*Nitrogen in Urine.*	*P_2O_5 in Urine.*	*$\frac{N}{P_2O_5}$.*	*Weight.*	*Remarks.*
	c.c.	Gm.	Gm.		Kg.	
1	120	1·86	0·34	5·40	7·300	—
2	130	1·33	0·39	3·40	7·150	—
3	110	1·34	0·36	3·70	7·000	—
4	205	1·04	0·36	2·90	6·850	—
5	220	1·26	0·21	6·10	6·750	15 milligrammes pilocarpine.
6	250	1·26	0·33	3·80	6·000	—
7	1,080	3·02	0·61	4·50	6·200	—
8	350	9·99	0·46	2·20	6·125	—
9	200	1·47	0·35	4·20	6·110	—
10	85	1·27	—	—	6·050	—

Here the rise reached 500 per cent. In another dog in nitrogenous equilibrium it rose to 25 per cent.

The excretion of phosphorus is also increased, but not to the same extent.

The explanation cannot be given off-hand. Probably the poison produces an increased destruction of glandular tissue, which, however, is not at once converted into the end-products. There is no connection between the nitrogen excretion and the diuresis, as their maxima do not coincide.

Atropine simultaneously administered prevents, among other effects, the increased elimination of nitrogen, as does also a liberal supply of carbohydrate food. Apparently this renders possible the resynthesis of the protein from its decomposition products. For the same reason the protein katabolism is less in animals which are well fed. Large doses (0·1 to 0·2 gramme) in dogs give rise to a marked loss of glycogen in the liver—in one case from 4·58 per cent. down to 1·2 per cent. (in thirty minutes ?), and in another from 1·6 per cent. to nil. Hyperglycæmia (from 0·08 per cent. to 0·164 per cent.) results, but not apparently in sufficient degree to produce glycosuria (3).

XIV.—ATROPINE.

Eichelberg states that single small doses in dogs do not influence protein metabolism; larger ones increase it (2). In starved and fed dogs 2 milligrammes produced no change, whereas 10 milligrammes acted like pilocarpine in producing a marked increase in P_2O_5.

De Stella obtained very different results by injections and instillations of 1 milligramme scopolamine, prolonged over considerable periods. There was a marked decrease during a week.

The details are given in the following table:

Animal.	*Weight.*	*Decrease in Percentages compared with Previous Period.*			
		Nitrogen.	Cl.	P_2O_5.	Volume of Urine.
	Kg.				
Rabbit ..	2·3	27	39	38	28
	2·3	15	15	28	17
Dog	2·5	20	28	16	19
	4·0	23	15	10	6

Although these results are very uniform, various circumstances warn us against too implicit confidence in them. In the first place, it is very remarkable that a rabbit on a daily diet of 200 grammes of carrots and 56 grammes of oats should excrete as much as 0·48 gramme of phosphates in the urine. Then, apart from the difficulty of carrying out exact metabolism experiments on dogs of 2·5 and 4 kilogrammes, it is not easy to understand how, with an intake of 200 c.c. milk and 150 grammes bread (and consequently about 4·2 grammes nitrogen), they could normally excrete on an average only 1·6 grammes nitrogen in the urine. Such an extreme nitrogen retention is only usual in growing animals.

In the case of acute atropine-poisoning glycosuria was observed, and after its disappearance alimentary glycosuria was easily produced (5). Enormous doses (5 to 1·0 grammes) produced glycosuria in four out of five rabbits.

LITERATURE.

1. Frank u. Voit: Die Wirk. von Pilokarpin auf die Zersetzungen im tier. Organismus. Z. B. **44.** 111. 1903.

2. Eichelberg: Ueber den Einfl. der Drüsengifte Atropin und Pilokarpin auf den Stoffwechsel, etc. Diss. Marburg, 1903.

3. Doyon et Kareff: C. r. S. B. **56.** 591. 1904.

4. De Stella: Étude pharmacodynam. de la scopolamine et de l'hyoscine. Arch. de pharmacodyn. **3.** 381. 1897.

5. Raphael: Glykosurie bei Atropinvergift. D. m. W. **1899.** 451.

XV.—CURARE.

It is of much importance to determine the influence of curare on metabolism, because in the first place the drug is of much pharmacological value, and, furthermore, it is necessary to distinguish any difference in metabolism which may occur in a curarized animal and one which is kept quiet by other means. We shall here deal only with the changes which occur independently of the respiratory paralysis.

Reliable methods showed a fall of about 50 per cent. in the oxygen intake and CO_2 output in a curarized rabbit (1, 2). A comparison of the excretion of normal and curarized animals gave about 35 per cent. decrease in katabolic changes (3). But recent very exact experiments on dogs have produced quite different results (4, 5). The main difference in the experimental conditions lies in the fact that the animals, which are in a state of muscular relaxation, and kept alive by artificial respiration, are supplied with the proper amount of heat to keep them at a normal temperature, in spite of the excessive heat loss induced by the curare. Under these circumstances it is found that, as soon as the functional activity of the muscles has been inhibited, increasing the dose of curare has no further influence on metabolism, and the CO_2 output remains the same for hours.[1] Only if the dose is large enough to produce a lowered blood-pressure does a further decrease in CO_2 output take place, apparently as a consequence of some unknown action.

The general result of these researches is that the metabolism of one and the same animal remains about the same, whether it is at rest (without muscular relaxation) or fully curarized (with muscular relaxation). For example :

Number of Experiment.	*Initial Temperature (Centigrade).*	*Normal.*		*Curarized.*	
		CO_2 per Hour in c.c.	Body Temperature (Centigrade).	CO_2 per Hour in c.c.	Body Temperature (Centigrade).
11	20·2°	13·00	38·45°	14·41	38·44°
7	19·8°	12·43	38·70°	12·11	38·80°
3	18·3°	12·65	—	13·10	38·16°
16	18·5°	12·95	39–38·4°	13·66	38·95°
5	18·3°	10·40	38·60°	10·45	38·72°
Average	—	12·29	—	12·73	—

In no case was the CO_2 output in the curarized animals less than normal ; often it was greater. From this we might draw the physiologically interesting conclusion that the muscle tone due to central excitation in a normal animal when at rest does not require a greater expenditure of energy than the purely peripheral muscle tone which remains when all central impulses are intercepted. But, in fact, this is

[1] Further, it appears that slight rigors do not appreciably increase the CO_2 output.

not a tenable position. In the first place, the fact that a muscle lengthens after section of its nerve is, to a certain extent, against it; in the second place, the experiments may be otherwise interpreted. The cutting off of the central impulses from the muscle, and the consequent decrease in the oxidation processes in the muscles, is overcompensated by the increase in heat production which occurs in order to equalize the increased heat loss. The increase is at first insufficient, or there would be no fall of temperature. This would be very likely more than enough to equal the CO_2 production of a normal resting animal.

The nitrogen output, as an index of protein metabolism, is not quantitatively changed. During the curarization there is a temporary delay, owing to interference with the excretory mechanism, and less nitrogen appears in the urine. The deficit is soon covered by subsequent production and elimination.

LITERATURE.

1. Röhrig u. Zuntz: Zur Theorie der Wärmeregul. und der Balneother. Ar. P. M. **4.** 57. 1871.
2. Zuntz: Ueber den Einfl. der Kurarevergift. auf den tier. Stoffwechsel. Ar. P. M. **12.** 522. 1876.
3. Pflüger: Wärme und Oxydation der lebenden Materie. Ibid. **18.** 247. 1879.
4. Frank u. Gebhard: Die Wirk. von Kurare auf die Aussch. der Kohlensäure und des Stickstoffs. Z. B. **43.** 117. 1902.
5. Frank u. Voit: Der Ablauf der Zersetz. im tier. Organismus bei der Ausschaltung der Muskeln durch Kurare. Z. B. **42.** 309. 1901.
6. Voit: Ueber die Wirk. der Temp. der umgebenden Luft auf die Zersetz. im Organismus der Warmblüter. Z. B. **14.** 57. 1878.

XVI.—ADRENALIN.

The glycosuria produced by the subcutaneous injection of extract of the suprarenal capsules (1, 3) is due to the presence of adrenalin, but is apparently independent of the rise of blood-pressure. For whereas the latter effect is well marked only when the adrenalin is given intravenously, sugar, according to most authors, is only found in the urine after subcutaneous or intraperitoneal injections. It must remain undecided why many authors also observed glycosuria after intravenous injections (8, 11, 14), as the different effects of subcutaneous and intravenous injections are easily and definitely demonstrable.

The glycosuria occurs more easily when the animal is well fed; but it can certainly be produced in starving animals [Noël Paton and others]. It does not, however, appear in animals after the glycogen has been removed, as Noël Paton (6) asserted. Loewy, in an unpublished research, has noted that by a combination of starvation and phlorizin—by which the last traces of sugar are got rid of—no more appears in the urine.

The effect of pyrexia, either from infection or puncture of the brain, on the sugar output has also been studied (10 to 12). Richter found that infection prevented glycosuria, but that the pyrexia of cerebral

puncture was without effect. Aronsohn, on the other hand, found that the latter inhibited glycosuria. Ellinger and Seelig were unable to confirm this. They found (as did Richter) that the glycosuria was not so great after the puncture, and that the effect attributed by Richter to an infectious fever was due apparently to a renal lesion to which could be assigned the major part in inhibiting glycosuria.

The proximate cause of the glycosuria is hyperglycæmia (2 to 8). It occurs even after a preliminary extirpation of the kidneys. The hyperglycæmia is dependent on the conversion into sugar of the liver glycogen (9).

In relation to the pancreas, the following facts are established: Painting the pancreas with adrenalin solution produces a very marked glycosuria (13); a rapid glycosuria was produced in a dog not previously glycosuric, in which the pancreas had been completely (?) removed (14), and the injection of adrenalin into ducks also produced glycosuria (2).

Little is known as to the other effects of adrenalin on metabolism. Apparently protein metabolism is quantitatively unaltered in dogs and birds, but in the latter the NH_3 excretion is increased somewhat at the expense of the uric acid.

Adrenalin in large doses induces atheromatous changes in vascular tissues, and through this indirectly affects metabolic changes.

LITERATURE.

1. Blum: Ueber Nebennierendiab. D. Ar. M. **71.** 146. 1901.
2. Noël Paton: On the Nature of Adrenalin Glycosuria. J. P. **29.** 286. 1904.
3. Blum: Über Nebennierendiab. Ar. P. M. **90.** 617. 1902.
4. Metzger: Zur Lehre vom Nebennierendiab. Mü. m. W. **1902.** 478.
5. Zülzer: Zur Frage des Nebennierendiab. B. k. W. **1901.** 1209.
6. Noël Paton: Effect of Adrenalin on Sugar and Nitrogen Excretion in the Urine of Birds. J. P. **32.** 59. 1904.
7. Vosburgh and Richards: Experimental Studies on the Sugar Content and Extravascular Coagulation Time of the Blood after Adrenalin. A. J. P. **9.** 35. 1904.
8. Loeper et Crouzon: L'Action de l'Adrénaline sur le Sang. Ar. m. ex. **16.** 83. 1904.
9. Doyon et Kareff: Action de l'Adrénalin sur le Glycogène du Foie. C. r. S. B. **56.** 66. 1904.
10. Richter: Fieber und Zuckeraussch. B. k. W. **1903.** 841.
11. Aronsohn: Die Zuckeraussch. nach Adrenalininjektion. Ar. p. A. **174.** 383. 1903.
12. Ellinger u. Seelig: Der Einfl. von Fieber, Infektion und Nierenschädigungen auf die Suprareninglykosurie. Mü. m. W. **1905.** Nr. 11.
13. Herter u. Wakeman: Ueber Adrenalinglykosurie und verwandte durch die Wirk. reduz. Subst. und anderer Gifte auf die Pankreaszellen hervorgerufene exper. Glykosurien. Ar. p. A. **169.** 479. 1902.
14. Lépine et Boulud: Ueber Adrenalinglykosurie bei Hunden nach Pankreasexstirp. Bull. de la soc. méd. d. Lyon. **1903.** 62.
15. Pearce and Baldauf: Vascular Lesions after Adrenalin Injections. A. M. J. S., 1906. **132.** P. 737.
16. Pearce and Stanton: Experimental Arterio-sclerosis. J. E. M., 1906. **8.** P. 74.
17. Berry: Influence of Adrenalin on Toxic Doses of Cocaine. A. M. J. S., Bd. 130, p. 893.

18. Cummins : Experimental Arterio-sclerosis. U. P. 1906. 19. P. 101.
19. Underhill and Closson : Adrenalin and Nitrogenous Metabolism. A. J. P. 17. 1906, p. 42.
20. Elliott and Durham : Subcutaneous Injections of Adrenalin. J. P. 34. 1906, p. 490.

XVII.—PHLORIZIN.

The most obvious effect is glycosuria. This must naturally have a secondary effect on metabolism. We must also inquire whether the phlorizin has any direct effect apart from, and independent of, the loss of sugar.

A.—THE BEHAVIOUR OF THE SUGAR IN THE BLOOD.

Since the discovery of phlorizin glycosuria—von Mering (1) showed that, in contradistinction to other known kinds of glycosuria, it occurs with an unchanged, or even a diminished, amount of sugar in the blood—many confirmatory experiments have been made [the blood sugar varies from 0·077 to 0·09 per cent. (2 to 7)]. But the conclusion has not remained unchallenged, as sometimes hyperglycæmia has been observed (6 to 9). This has in some cases [Wolen (6)] been due to the large amount of blood withdrawn (7, 10, 11, 65), which was enough in itself to produce hyperglycæmia in the remaining blood. Pavy (5), in his very careful experiments, was only able to demonstrate a very slight increase (0·08 to 0·149 per cent.), and does not appear to attach any importance to it as a cause of the glycosuria. The slight increase was probably due to the fact that the cats were in captivity. Others attribute the glycæmia to the large amount of blood withdrawn in some cases ; in others, exact details are wanting.

We can therefore regard it as an established fact that the glycosuria of phlorizin is not dependent on an increased amount of sugar in the blood ; a slight hyperglycæmia not casually related to the glycosuria may occur.

B.—THE PROXIMATE CAUSE OF THE GLYCOSURIA.

Von Mering supposed that the formation of the sugar must occur in the kidneys. In this case, after extirpation of the kidneys, the sugar in the blood should not rise above normal. This has been shown to be the case (2), in contradistinction to what happens when the pancreas is removed (5, 7, 12, 13, 64).

Furthermore, birds which do not exhibit glycosuria as a result of hyperglycæmia (14) regularly excrete sugar after phlorizin (15), which shows the independence of the two conditions.

Zuntz (10) demonstrated the part played by the kidney in a very original way. He injected phlorizin into the renal artery of one side, and observed that this kidney first excreted sugar into the urine. Working with the isolated kidney, Pavy and others found some sugar in the urine after perfusion with phlorizin. They do not state, however, whether any sugar was previously present in the urine. It is necessary to know this, as small amounts of sugar are said (16) to have been obtained from the urine after perfusion of the kidney with blood which were not increased by the addition of phlorizin. Recently, Brodie (17) has found sugar in the urine after perfusion with phlorizin and Ringer's solution (frogs' kidneys).

The general results are rendered more difficult to interpret by the observations of Levene, and Biedl and Kolisch, who found a slightly higher percentage of sugar in the renal veins than in the arteries—an amount so small as to be within the limits of experimental error.

In the first place, owing to the presence of sugar, there may have been an increased excretion of water, and estimations of the dried substance were not made. In the next place, the simultaneous disturbance of the arterial and venous circulation might easily affect pathologically an organ as sensitive to changes in its blood-supply as is the kidney.

C.—THE ACTION OF PHLORIZIN ON THE KIDNEYS.

As the amount of sugar in the blood is not increased, an increased permeability to sugar in the kidneys is assumed to result from phlorizin. It is easy to say this, but it is very difficult to get a satisfactory idea of how it happens. Minkowski (2) thought that phlorizin was decomposed in the kidney into phloretin and phlorose ; the latter was excreted, and the former combined with the blood sugar, but subsequently the combination was broken down, and so on, till by degrees all the phloretin was excreted or decomposed. Hence the kidneys were assumed to have the power of decomposing glucosides. It has long been thought that the kidney contained tissue enzymes (18, 19)—*e.g.*, one breaking down hippuric acid—and Charlier states that he has actually found that horse's kidneys can break up phlorizin. The extracts of other kidneys are inactive (5) ; but this is not actually against Minkowski's suggestion, as possibly the effect depends on the life of the kidney cells. On the other hand, the fact that phloretin is less powerful than phlorizin may be cited as against the correctness of the theory (20, 21).

According to the most recent view, the kidney, by means of the action of phlorizin, is enabled to detach the normally combined sugar from its combination, and thus makes its excretion possible. Independent observers have arrived at this conclusion by various ways [O. Loewi (22), Pavy and Siau (5)]. Loewi concluded that normally the sugar existed in the blood in combination, because its excretion by phlorizin is not increased by diuresis, in which it differs from grape-sugar artificially injected into the blood. The scope of this article will not allow a more

detailed discussion of this point. No objection to this view can be raised on the score of the fact that blood, when dialyzed against protein or protein-free fluids, can be rendered free from sugar (23, 24). The blood for the purpose of the experiment has been altered. It is acid, and defibrinated (25, 26). Probably a small portion of sugar is normally free in the blood, and thus a certain equilibrium is maintained. When this is removed, the equilibrium is disturbed, and can only be restored by some of the combined sugar being set free.

Brodie, Pavy and Siau, however, think that the action of phlorizin is not confined to this, but that under its influence not only is sugar formed from its combination in the blood, but by other ways also. This suggestion is so original and so important in principle that its experimental basis will need detailed examination.

The intestines, including the liver, were isolated, and the amount of sugar in the blood estimated. Phlorizin was then injected, and the sugar estimated again at the end of several hours. There was a decrease in the amount which was much less than would be expected, considering the amount which had meanwhile appeared in the urine. This appears to contradict what was hitherto regarded as self-evident—namely, that the sugar in the urine arises solely from that in the blood. The following result was particularly notable—namely, that after the isolation of the intestines the sugar in the blood fell almost to the same extent when no phlorizin was given and no glycosuria had occurred.

This seems to show that the sugar in the urine does not arise from that which can be demonstrated in the blood. This is the conclusion of these observers. They also believe that the kidneys have the power of forming sugar from the constituents of the blood. Either the sugar must exist in the blood preformed, but firmly combined, so that it cannot be estimated by our ordinary methods, or else only the materials for sugar synthesis are present, and this is carried out in the kidneys.

As, however, in these experiments the muscles could not be excluded, the following possibilities must be taken into account: To cover the loss of sugar either through the urine after phlorizin, or through the ordinary channels of consumption without phlorizin, in the absence of the usual compensating action of the liver, only the muscles can be employed. This activity is not sufficient to keep the sugar at its normal figure (at the end of the experiment it was lower than at the beginning), but would at least almost cover the loss of sugar by the kidney. In view of the fact that the sugar content in the blood was no higher without phlorizin than with it, some results of perfusion of the excised kidney may be compared [Pavy].

1. Perfusion of 400 c.c. blood with 0·132 per cent. glucose (=0·528 gramme). Result after three and a half hours:

140 c.c. blood with 0·056 per cent. glucose	= 0·079	gramme.
125 c.c. urine with 0·415 per cent. glucose	= 0·332	,,
Total	0·411	,,
Loss: 135 c.c. blood with	0·117	,,

In this case the sugar in the urine was fully compensated by that in the blood.

2. Perfused: 300 c.c. blood with 0·106 per cent. glucose = 0·318 gramme.
Recovered: 150 c.c. blood with 0·036 per cent. glucose = 0·054 ,,
85 c.c. urine .. .. = 0·349 ,,
0·403 ,,

Thus 0·403 – 0·318 = 0·085 gramme more was found than was originally present in the blood. The sugar in the kidneys and that in the blood contained in them was negligible.

3. Perfused: 350 c.c. blood with 0·197 per cent. glucose = 0·374 gramme.
Recovered: 200 c.c. blood with 0·045 per cent. glucose = 0·090 ,,
105 c.c. urine .. .. = 0·451 ,,
0·541 ,,

Then at the end of the experiment 0·541 – 0·374 = 0·167 gramme glucose more was found than was contained in the blood at the beginning of the experiment.

This result is most important, and can only be interpreted as showing that the sugar is formed from the blood in the kidney, for a little reflection will convince us that no previous storage of a precursor of sugar could exist in the kidneys. It would, however, be a bold thing to found an important fundamental theory on so few experiments, which, though carried out very carefully and accurately, showed such small differences in the resultant figures. Brodie and Cullis (17), however, have recently perfused frogs' kidneys with Locke's solution, which does not reduce, and contains no phlorizin, and have obtained a body in the urine which reduced Fehling's solution.

Levene had earlier stated that sugar was formed in the kidney, because, by injecting phlorizin into one kidney, he found more sugar there than in the other. But by these experiments he could not exclude the possibility of the excess of sugar being caused by the retention of the saccharine urine in the kidney.

We cannot now exclude the possibility that phlorizin causes the kidney to form sugar from other material than its combinations in the blood; but Pavy assumes that the latter furnish the main source for the sugar found in the urine. He supports this view by the important observation that in his perfusion experiments, when the secretion of sugar became low, it could again be raised by employing fresh blood. Two observations may also be here adduced. Hedon (27) found that hyperglycæmia following extirpation of the pancreas is reduced by phlorizin, and Lewandowsky that in phlorizin animals bleeding only produced its ordinary effect of hyperglycæmia after nephrectomy.

On the other hand, the fact that there is no rise in the sugar in the blood after extirpation of the kidneys without a considerable collection of glycogen taking place in the muscles and liver shows that, apart from its action on the kidney, phlorizin does not primarily increase the formation of sugar in the organism (unpublished research of Minkowski).

The change in the kidney is functional—that is to say, no microscopical changes can as yet be recognised. A few observers have noted gross pathological alterations, and others record the onset of albuminuria after phlorizin injections, but this is by no means usual (28, 29). Loewi has injected dogs every day for months, and kept them under observation for years without finding the least trace of albumin or casts, or other

signs of kidney damage, in the urine. In the cases cited there may have been complications—probably of the nature of septic infection—which had nothing to do with the phlorizin as such.

Spasms, vomiting, and other symptoms, which are often described as the results of phlorizin, can be avoided, even in experiments lasting for months, by care in performing the injections.

D.—CONDITIONS INFLUENCING THE AMOUNT OF SUGAR EXCRETED.

1. The Method of Administration.

If phlorizin is given by the mouth, the sugar excretion is decidedly less [von Mering]. Loewi showed that the cause of this is not an increase in protein destruction and sugar formation, but the fact that phlorizin is comparatively badly absorbed from the intestine (21). The fact that after small doses (1 gramme) no unchanged phlorizin is found in the intestine does not tell against this explanation (31, 32). The drug is broken up in the intestine, and the resulting product, which gives rise to glycosuria, is difficult to absorb. There is no evidence that the substance is fixed or broken up in the liver—at any rate, injections given hypodermically are as efficacious as those given directly into the portal vein. Apparently phlorizin acts in the organism as such, phloretin being less active.

2. The Vehicle.

It has been shown that an alcoholic solution (0·01 gramme in 4 c.c. 25 per cent. alcohol) acts more powerfully than the usual soda solution (1 gramme in 10 c.c. warm 1 per cent. soda) (33).

3. Dosage.

The size of the dose is of considerable importance to the amount of sugar excreted, which, *cæteris paribus*, depends upon this. Lusk (34), following a suggestion of Cremer's (30), showed, in a very careful research, that, with a constant diet, a maximal excretion was obtained with three subcutaneous injections at equal intervals. The excretion of sugar could not then be increased within twenty-four hours. The size of the single doses required to produce a maximal effect depends, firstly, on the idiosyncrasy of the animal, and must be determined experimentally in each case; secondly, on the amount and character of the material supplied for sugar formation—that is to say, after the most effective dose with a given diet has been determined, an increase in the food must be made as well as an increase in the drug (21). The type of sugar-producing material is also of importance (35). The table on p. 1188, which has not been previously published in full, shows how complicated are the conditions.

A dog, weighing 25·5 kilogrammes, was given an injection of phlorizin and 200 grammes meat thrice daily at intervals of eight hours.

Date.	*Nitrogen.*	*Sugar.*	*Phlorizin.*	$\frac{N}{Sugar}$	*Increase in Sugar.*	*Remarks.*
1902.	Gm.	Gm.	Gm.		Gm.	
March 9–10	18·73	54·40	3×0·5	1 : 2·9	—	—
,, 10–11	18·58	50·87	3×0·5	1 : 2·7	—	—
,, 11–12	20·70	59·90	3×1·0	1 : 2·9	—	—
,, 12–13	18·82	55·96	3×1·0	1 : 3·0	—	—
,, 13–14	—	—	—	—	—	Not analyzed.
,, 14–15	18·73	58·41	3×1·0	1 : 3·1	—	—
,, 16–17	22·18	67·86	3×1·0	1 : 3·0	—	—
,, 17–18	17·89	57·33	3×1·0	1 : 3·2	—	—
,, 18–19	22·06	89·60	3×1·0	1 : 4·1	17·9	50 gm. sugar extra in one dose.
,, 19–20	18·48	60·84	3×1·0	1 : 3·3	—	—
,, 20–21	20·38	82·68	3×1·0	1 : 4·1	16·4	50 gm. sugar extra in three doses.
,, 21–22	19·65	63·18	3×1·0	1 : 3·2	—	—
,, 22–23	18·70	78·00	3×2·0	1 : 4·2	—	—
,, 23–24	22·06	101·40	3×2·0	1 : 4·7	9·9	50 gm. sugar extra in one dose.
,, 24–25	18·96	78·39	3×2·0	1 : 4·1	—	—
,, 25–26	18·17	79·10	3×2·0	1 : 4·2	—	—

This table shows the dependence of the amount of the sugar excretion on the size of the dose of phlorizin. It also shows clearly the influence of the kind of material from which the sugar is formed. On March 18 and 20, 50 grammes of glucose were added to the diet, and the sugar excretion rose to 89·6 and 82·79 grammes respectively. This amount, apparently, could be dealt with by the kidneys, but only when the glucose itself was increased. The sugar excretion arising from meat had amounted to between 56 and 68 grammes per diem with 3 grammes of phlorizin ; but in order to increase this to a like extent, the dose had to be increased to 6 grammes. The cause of this peculiar difference, which has not previously been noted, cannot be stated. The following possibilities may be considered : The formation of sugar with 3 grammes of phlorizin may have been as great as with 6 grammes, and the excretion only have been less, possibly because the maximal phlorizin action was not simultaneous with the sugar formation, and so a part of the latter was oxidized ; or the sugar formation may have been less with 3 grammes, so that less was passed on to the kidneys.

No definite decision can be made. Finally, we must remember that sugar may reach the kidney in various forms, according to the substance in which it originates. Comparing Pavy's views as given above, the difference could easily be understood if, with him, we assume that the kidneys do not only excrete sugar from the preformed, easily recognisable sugar in the blood, but also from material of quite another kind.

The power of thus forming sugar might well be much less than the power of splitting off the preformed sugar, and depend entirely on the severity of the poisoning, which possibly cannot exceed a certain limit.

4. The Dependence of the Amount of Sugar Excretion on Diet.

(*a*) *Starvation.*

Starving animals excrete large amounts of sugar under the influence of phlorizin. Glycosuria will occur even after ninety days' fast [Lusk and others (36 to 38)].

With regular eight-hourly subcutaneous injections there is at first much more sugar excreted than later, when the amount becomes fairly regular and constant (39). This constant, however, is not an absolute one, but is rather relative to the amount of nitrogen simultaneously excreted. The increased excretion which takes place at first—as is also seen after extirpation of the pancreas—is commonly regarded as a " flushing out " of the sugar present in the organism, whether preformed or derived from glycogen as a result of the loss of that previously present in the blood. The " flushing-out " process is due to a stimulation of the glycogenic function of the liver by the low sugar content of the blood, which, again, depends on the excretion of sugar in the urine. As a matter of fact, no glycogen is found in the liver when phlorizin glycosuria is at its height (*vide supra*). If the decrease in the sugar in the blood is prevented by removal of the kidneys, a considerable amount of glycogen is found in the liver (unpublished research). The small glycogen content of the phlorizin liver has been much disputed, as, under certain circumstances, noticeable amounts have been found. It is of importance, as regards the elucidation of various points, to decide whether the liver is free from glycogen or not, and so it will now be discussed in more detail. The liver of starving animals—or, within certain limits, of animals on a flesh diet—is practically free from glycogen in a short time—that is to say, when an equivalent amount of sugar has been excreted. Assuming that the maximal action of phlorizin is maintained (which it seldom is, owing to the inconvenience of making injections every eight hours), only traces of glycogen can be found in a dog's liver—namely, 0·08 to 0·13 per cent. [Lusk (34)], and 0·04 to 0·08 per cent. [Loewi (unpublished experiment)]. On the other hand, considerable amounts have been found when the drug was given by the mouth, or when the full toxic action was not secured, or when the analysis was made during the decline, and not at the height, of the process. In this case, as is well known, fresh glycogen is formed (40 to 43). Glycogen may very easily be demonstrated in larger amounts when narcotics are employed which prevent its utilization by the organism.

That this is the *rationale* of the initial increase in the sugar excretion is shown by the fact that a transient increase in sugar excretion occurs when, after a submaximal dose, the amount of phlorizin is increased, while the diet remains constant. This sugar represents, of course, the amount which has escaped oxidation during the intervening period.

The amount of sugar excretion during starvation corresponds to the nitrogen excretion, being at first constant, but rising just before death. This means that, as a rule, in the same animal the ratio between nitrogen and sugar excretion is practically constant. In dogs it is generally 1 : 3·75. In some experiments considerable variations have been found, the extremes being 2·75 and 4·2. The cause of these variations is unknown. The lower amounts have been attributed to a damaged condition of the kidney. There is no doubt that kidney lesions influence the amount of sugar excretion in phlorizin-poisoning (44 to 46), as in other forms of glycosuria (47). But we must not consider this the cause of all the low ratios of sugar to nitrogen. The facts that in certain animals the sugar output is low from the first, and remains low throughout, and that often no traces of any kidney lesion, such as albuminuria or casts, can be found, negatives this view, which was originally put forward by Lusk and Stiles (48).

In cats (39), goats, and rabbits, the ratio of sugar to nitrogen is generally 1 : 2·8. The cause of this difference between dogs and other classes of experimental animals is obscure.

When we deal with the influence of various classes of food-stuffs on the amount of sugar excretion, we shall be in a position to determine from what material the sugar excreted during starvation arises.

(*b*) *Diet.*

In order to estimate the influence of any particular food-stuff on the amount of sugar excretion, it is essential that the phlorizin should produce a maximum effect, and that the substance to be tested should not be given until a constant sugar excretion has been obtained. Otherwise it is impossible to decide whether the whole or part of the food-stuff is not used up in the organism itself, either immediately or as a reserve. The food-stuff, again, must not be given to an animal which has already reached the highest possible limit of sugar excretion.

(i.) *Carbohydrate.*

Glucose added to the diet, or injected subcutaneously under the conditions mentioned above, increases the sugar excretion. With doses of 24 grammes the increased output about corresponds to the intake.

Example: Bitch; 1·5 grammes phlorizin thrice daily; May 5, 1901; starved.

Date.	*Injection.*	*Nitrogen.*	*Sugar.*	*Ratio.*	*Remarks.*
		Gm.	Gm.		
June 12 ..	1	3·15	10·92	1 : 3·4	—
	2	3·29	10·53	1 : 3·2	—
	3	3·22	10·92	1 : 3·3	9 gm. glucose by œsophageal tube
„ 13 ..	1	2·86	19·11	1 : 6·6	—
	2	2·92	10·53	1 : 3·6	—
	3	2·69	10·53	1 : 3·8	—

With doses of 50 grammes only a portion reappears in the urine, even when the phlorizin is increased. What, then, happens to the remainder which is not excreted ? It is, apparently, disposed of in the ordinary manner—that is, used when wanted, and when not wanted is stored up. The difference in the fate of large and small doses of sugar can be explained as follows : The power of the kidney to split off sugar from the material which is circulating in it is, of course, limited. At first this material is the sugar in the blood. When the proportion in the blood falls owing to excretion, the liver converts glycogen till the normal amount is restored. This continues as long as the kidney excretes sugar, and when all the glycogen in the liver is used up, other organs supply the material for sugar formation. The rapidity with which the sugar lost in the urine is replaced depends, of course, on the activity of sugar formation and the metabolism of the organs. With a certain amount of poisoning, apparently the sugar supply is not as much as the kidney is capable of managing. If more sugar is introduced by the mouth, the replacement of blood sugar, of course, takes place more rapidly than before, more sugar reaches the kidney in a given time, and more is excreted.[1] When the excreting capacity of the kidney is exceeded, the sugar must, as has been pointed out, either be utilized in the ordinary way, or remain unoxidized, owing to some secondary disturbance unconnected with the renal function. The following facts render the second view untenable : Large doses of sugar in phlorizin-poisoning are capable of sparing protein. When the poisoning is insufficient, an addition to the dose does not produce a greater excretion of sugar ; and, lastly, after extirpation of the kidneys, the sugar in the blood does not increase, though there is no noticeable accumulation of sugar in the liver.

In addition to glucose, lævulose and galactose cause an increase in the sugar excretion which corresponds to their dextrose moiety.

Throughout it has been tacitly assumed that sugar taken in as food affords immediate material for excretion, and not that it is really oxidized at once, so rendering material from other sources available for sugar excretion. This latter assumption is unnecessary, since it has been shown that glycogen accumulates in the liver when it is perfused with blood containing sugar in solution (49).

(ii.) *Fat.*

Neither free fatty acids (50) nor their glycerides increase sugar excretion. The apparently contradictory experimental results (51) are not of any great importance, as, in the first place the figures vary excessively, and, in the second place, as Lusk and Stiles rightly remark, the ingestion of enormous quantities of fat may well have set up marked fatty acid diarrhœa, whereby glycerin would be set free for the formation of sugar, a process undoubtedly possible (52, 53).

[1] We need not suppose that small amounts of sugar in phlorizin-poisoning circulate in an unoxidizable form (48), which would imply some disturbances quite independent of the action of the kidneys.

(iii.) *Protein and its Derivatives.*

If protein is given to a fasting animal after poisoning it with phlorizin and estimating the sugar excretion, the excretion rises with that of the nitrogen, and in a constant ratio. This ratio is the same as that which obtains during starvation. We cannot at present say whether all forms of protein behave in the same manner. Casein, egg-white, and fibrin, have hitherto been investigated (66). Gelatin added to the diet has the same effect as albumin. Conjugated proteins, the combined end-products of pancreatic digestion (61),[1] and amino-acids also raise the sugar excretion. Only leucin and asparagin have been tested, but the others probably act in the same way, as glycocoll and alanin in pancreatic diabetes increase the glycosuria like asparagin. Uric acid has no influence on sugar excretion. How protein diet increases glycosuria is one of the most debated points in metabolism. The following are possible hypotheses :

1. Protein is a direct antecedent of sugar—that is, a part of it either alone or in conjunction with parts of the cell protoplasm can give rise synthetically to sugar. This is not only a separating out of a preformed carbohydrate group, as such a group is absent in many proteins which, nevertheless, increase glycosuria ; and in other forms of protein this increase is greater than would correspond to the amount of carbohydrate calculated to be present.

2. Protein is an indirect antecedent of sugar. As protein increases glycosuria in glycogen-free animals poisoned by phlorizin, an indirect action can only mean that it causes a formation of sugar from fat or from some unknown substance. The possibility of this cannot be denied, though it appears hardly probable (57). It need not be further discussed here, as it is dealt with in two other places [Magnus-Levy (54), von Noorden (55)].

Certainly no overwhelming evidence exists either for the direct or indirect formation of sugar from protein. Embden's recent and remarkable researches are of much importance in this connection, as they show how carbohydrate can be formed from fat as well as from protein (56).

E.—PROTEIN METABOLISM.

It is obvious that an extreme carbohydrate[2] loss, such as can only be induced by phlorizin under conditions of inadequate nourishment, must considerably affect protein metabolism. On the one hand, the loss of sugar occasions a loss of fuel, which must be made up by protein ; and, on the other hand, some special damage is probably set up, owing to the cell protoplasm having lost the power of seizing and retaining one of its constituent groups.

[1] These give the same ratio of sugar to nitrogen as meat.

[2] In healthy persons the withdrawal of carbohydrates from the diet does not absolutely deprive the organism of carbohydrate, as the albuminoid bodies (in the widest sense of the term) contain appreciable amounts.

Besides this, however, a primary disturbance may be occasioned by phlorizin somewhat similar to that set up by phosphorus. We will now consider if there is any ground for this assumption.

The question can only be answered by experiments in which we can be sure that we are dealing solely with the action of phlorizin. This can be secured by administering the drug *per os*. To this, however, there is the objection that it does not produce so marked an action as subcutaneous injection. The latter requires most laborious observation if all the possible complications are to be excluded.

One of the most important is the rise of temperature which frequently occurs, which of itself gives rise to increased protein katabolism. The following table illustrates the differences in the two forms of administration (21):

Large bitch, weight 17·67 kilogrammes. Catheter every twenty-four hours. Food, 500 grammes meat (16 grammes nitrogen). Water *ad lib.*

Date.	Amount of Urine.	Nitrogen.		Sugar.		Remarks.	Temperature, C.
		Per Diem.	Average.	Per Diem.	Total.		
1900.	c.c.	Gm.	Gm.	Gm.	Gm.		
January 14	290	12·94	—	—	—	—	—
,, 15	345	14·67	14·45	—	—	—	—
,, 16	480	14·17		—	—	—	—
,, 17	340	14·45		—	—	—	—
,, 18	420	14·50		—	—	—	38·4°
,, 19	455	15·01	15·06	18·72	52·8	3 × 2 grammes phlorizin *per os*	38·6°
,, 20	480	15·12		28·08			38·5°
,, 21	300	14·70	14·94	6·00	—	—	38·9°
,, 22	320	15·68		—	—	—	38·3°
,, 23	380	14·56		—	—	—	38·4°
,, 24	500	15·08		—	—	—	38·3°
,, 25	500	14·00		—	—	—	38·5°
,, 26	470	15·83		—	—	—	38·3°
,, 27	830	17·86	17·43	90·48	126·4	3 × 2 grammes phlorizin subcutaneously	38·3°
,, 28	490	16·97		35·88			39·5°
,, 29	315	12·94	14·77	—	—	—	38·5°
,, 30	400	15·57		—	—	—	38·3°
,, 31	390	15·79		—	—	—	38·4°

The result of the first method of giving phlorizin shows that with an adequate diet an effective dose of phlorizin is without influence on the protein katabolism. Substances like phosphorus, which have a primary action in increasing it, do not give a result like this. Moritz and Praussnitz (58) obtained like results by means of very exact experiments, and came to the conclusion that protein metabolism was not affected in starved animals. When the diet is sufficient to make up for the loss of calories, no protein loss occurs. Carbohydrates and fats have the same protein-sparing action as in normal animals.

When phlorizin is given subcutaneously the protein katabolism is not raised, except when the diet is inadequate. If this were invariably the case, we might assume that, apart from complications, phlorizin had no specific action, as there is always the possibility that it is not absorbed in the same form subcutaneously as from the stomach. But in many cases the nitrogenous equilibrium is not disturbed. The following figures show what considerable variations may occur :

Author.	*Food.*	*Animal.*	*Weight.*	*Average per Diem.*	
				Nitrogen.	Sugar.
			Kg.	Gm.	Gm.
Lusk	Meat 300 grammes	Dog A	21·4	18·3	69·3
	,, 300 ,,	,, B	27·3	11·9	45·4
Loewi	,, 500 ,,	,, A	21·1	31·7	98·0
	,, 500 ,,	,, A	24·0	19·1	68·8

The table quoted on p. 1188 also shows that nitrogenous equilibrium may remain undisturbed. There is no analysis of the fæces, but this is unnecessary with subcutaneous injections.

We must therefore conclude that phlorizin has no toxic power of producing protein decomposition. When increased protein excretion is noticed, it is secondary either to loss of sugar or to complications such as pyrexia.

F.—GENERAL METABOLISM.

The results of a number of investigations show that no change is produced by phlorizin, but the results are not above suspicion (13, 50, 60, 61).

Lusk compared the total metabolism of a starving dog before and after phlorizin :

	Normal Dog.			*Phlorizin Dog.*		
	Protein.	Fat.[1]	Total.	Protein.	Fat.	Total.
	Gm.	Gm.	Gm.	Gm.	Gm.	Gm.
Oxidized	20·19	55·87	—	67·38	51·15	—
Calorie value ..	80·68	526·13	606·81	124·08	481·69	605·77

Lusk and Mandel's results were similar. The experiment began on the fifth day of starvation.

[1] Calculated.

Dog weighing 14·2 Kilogrammes.

Date.	Nitrogen.	Carbohydrate.				Calories.			Food.
		In Urine.	Expired.	Total.	Calculated from Fat.	From Protein.	From Fat.	Total.	
1903.									
February 20	1·85	1·35	32·21	33·56	27·46	46·2	338·0	384·2	Starved.
,, 21	1·53	1·12	30·96	32·08	27·03	38·3	332·7	371·0	,,
,, 22[1]	3·83	8·39	28·93	37·32	24·60	44·2	302·8	347·0	,,
,, 23[1]	7·00	15·24	29·96	45·20	22·29	80·2	274·4	354·6	,,
,, 24[1]	12·94	26·75	31·05	63·83	21·26	161·9	261·7	423·6	300 gm. fat.
,, 25[1]	11·22	23·21	38·78	61·96	25·15	140·4	309·5	449·9	300 gm. fat, 309 gm. meat.
,, 26[1]	6·64	14·53	33·78	48·30	26·45	76·5	325·6	402·1	Starved.

The estimation of the calories in both experiments was made on the supposition that no oxidation of sugar took place.

Both showed that the calorie values were practically unaltered, the increased excretion of unoxidized sugar in the urine being fully compensated by an increased protein katabolism. The oxidation of fats was always decreased.

A further experiment, on the other hand, gave the following result :

Dog weighing 17·6 Kilogrammes.

Date.	Nitrogen.	Carbohydrate.				Calories.			Food.
		In Urine.	Expired.	Total.	Calculated from Fat.	From Protein.	From Fat.	Total.	
1903.									
April 20	4·14	3·02	60·80	63·82	50·20	103·42	617·98	721·38	Starved.
,, 22[1]	15·50	31·76	70·22	101·98	54·28	166·90	668·18	835·08	,,
,, 23[1]	12·75	27·89	67·26	95·15	53·20	144·75	656·12	800·87	50 gm. meat, 100 gm. fat.

Here the calories used up under the influence of phlorizin showed an increase, and at the expense of the protein.

The table on p. 1196 gives the result of an experiment by Rubner.

Here again was an average rise of 32·2 calories. Rubner calculated that the increase corresponded to the amount of heat set free by the extra protein katabolism on the days when phlorizin was administered.

The general conclusion is, then, as follows : The loss of calories due to the sugar excretion is made up for by increased protein katabolism. As every increase in protein katabolism increases the heat production (the specific dynamic action of protein), so oxidation processes in phlorizin glycosuria are raised only in correspondence with the amount of

[1] Phlorizin.

increased protein katabolism. There is no specific action on katabolism apart from the effect of increased sugar excretion.

Dog weighing 10 Kilogrammes.

Day of Starvation.	Nitrogen.	Carbohydrate.					Calories.			
		In Urine.	In Fæces.	Expired.	Total.	Calculated from Fat.	Protein.	Fat.	Sugar.	Total.[1]
6	3·10	2·25	0·07	41·20	44·1	34·3	77·5	421·8	—	499·3
7	2·51	1·86	0·07	37·40	40·2	32·0	62·7	393·6	—	456·3
8[2]	6·00	4·40	0·07	51·80	56·9	37·2	150·0	440·6	23·93	500·1
9[2]	7·71	5·50	0·07	52·91	59·1	33·8	192·5	415·7	23·40	520·3

G.—FATTY INFILTRATION OF THE ORGANS.

The liver is remarkably rich in fat (63). As against a normal fat content of about 10 to 15 per cent. (reckoned as dry substance), in phlorizin livers as much as 25 to 75 per cent. has been found. This disappears spontaneously when the poison is withheld, or when there is a plentiful supply of glycogen-forming meat or sugar. An interchangeability between fat and glycogen has been suggested, as the fat makes its appearance just when the glycogen has disappeared. As with phosphorus-poisoning, the more intimate changes which occur are obscure. Numerous experiments with mutton-fat show that the substance is brought into the liver from without. No infiltration of the lungs or kidneys occurs.

H.—ACIDOSIS.

Acetone bodies occur in the urine of men and monkeys (67) as soon as the carbohydrates in the diet fail. This does not occur in dogs or such other animals as have hitherto been observed unless there is still further loss of sugar. Recent confirmatory experiments have shown that in addition there must also be a loss of nitrogenous equilibrium (1, 60), as when, together with the phlorizin-poisoning, there is a deficiency in protein nourishment.

Summary.

Phlorizin produces an excretion of sugar by means of its special action on the kidneys, in consequence of which the liver loses its glycogen and becomes the seat of fatty infiltration. There is also a loss of calories, owing to the excretion of sugar, which is covered by increased protein katabolism. There is no evidence of any disturbance independent of the action on the kidneys.

[1] After deducting sugar calories. [2] Phlorizin.

LITERATURE.

1. von Mering: Ü. Diab. mell. Z. M. **14.** 405. 1888; and **16.** 431. 1890.
2. Minkowski: Über den Diab. mell. nach Exstirp. des Pankreas. E. A. **31.** 85. 1893.
3. Levene: Phlorhizinglycosuria. J. P. **17.** 259. 1894.
4. von Czyhlarz u. Schlesinger: Blutzuckerbestim. bei Phlorhizindiab. W. k. R. **1901.** 41.
5. Pavy, Brodie, and Siau: Mechanism of Phlorhizin Glycosuria. J. P. **29.** 467. 1903.
6. Coolen: L'action physiol. de la phlorhizine. Arch. de pharmacod. **1.** 267. 1894.
7. Lewandowsky: Phlorhizindiabetes. D. A. **1901.** 365.
8. Pavy: On Phloridzin Diabetes. J. P. **20.** 22. 1896.
9. Biedl u. Kolisch: Phlorhizindiabetes. K. i. M. **1900.** 573.
10. Zuntz: Phlorhizindiabetes. D. A. **1895.** 570.
11. Rose: Der Blutzuckergeh. des Kaninchens, seine Erhöhung durch Aderlass, etc. E. A. **50.** 15. 1903.
12. Schabad: Phlorhizinglykosurie bei künstl. hervorgerufener Nephritis. W. m. W. **1894.** 108.
13. Uschinsky: Ueber den Gaswech. und die Kalorimetrie bei Hunden, welche mittels Phlorhizin diab. gemacht wurden. Ar. m. ex. **5.** 545. 1894.
14. Kausch: Ü. den Diab. mell. der Vögel nach Pankreasexstirpation. E. A. **37.** 274. 1896.
15. Thiel: Exper. Glykosurie bei Vögeln. Diss. Königsb., 1887.
16. Charlier: Sur le dédoublement de la phlorhizine au niveau du rein. C. r. S. B. **53.** 494. 1901.
17. Brodie and Cullis: On the Secretion of Urine. J. P. **34.** 224. 1906.
18. Schmiedeberg: Ueber Spaltungen und Synthesen im Tierkörper. E. A. **14.** 371. 1881.
19. Minkowski: Ueber Spaltungen im Tierkörper. E. A. **17.** 445. 1883.
20. Lusk: Ueber Phlorhizindiab. Z. B. **36.** 82. 1898.
21. Loewi: Phlorhizindiabetes. E. A. **47.** 48. 1901.
22. Loewi: Physiol. und Pharm. der Nierenfunktion. E. A. **48.** 410. 1902.
23. Asher u. Rosenfeld: Ueber das physik.-chem. Verhalten des Zuckers im Blute. C. P. **19.** Nr. 14. 1905.
24. Schenk: Ueber das Verhalten des Traubenzuckers zu den Eiweisskörpern des Blutes. Ar. P. M. **46.** 607. 1890.
25. Zuntz: Beitr. zur Physiol. des Blutes. Diss. Bonn, 1870.
26. Winternitz: Alkaleszenz des Blutes. Z. p. C. **15.** 506. 1891.
27. Hédon: Action de la phlorhizine chez les chiens diab. par l'exstirp. du pancréas. C. r. S. B. **49.** 60. 1897.
28. Trambusti u. Negri: Phlorhizindiabetes. Be. A. P. **14.** 337. 1894.
29. Kossa: Die Wirk. des Phlorhizins auf die Nieren. Z. B. **40.** 324. 1900.
30. Cremer u. Ritter: Phlorhizinvers. am Karenzkaninchen. Z. B. **29.** 256. 1893.
31. Moritz u. Praussnitz: Phlorhizindiabetes. Z. B. **27.** 81. 1890.
32. Külz u. Wright: Die Wirkungen des Phlorhizins und Phloretins. Z. B. **27.** 181. 1890.
33. Knopf: Phlorhizindiabetes. E. A. **49.** 123. 1903.
34. Lusk, Reilly, Nolan: Phlorhizindiabetes in Dogs. A. J. P. **1.** 395. 1898.
35. Loewi: Unpublished research.
36. Cremer: Phlorhizinvers. am Karenzkaninchen. Mü. m. W. **1893.** 14.
37. Halsey: Ueber Phlorhizindiab. bei Hunden. Sit. M. **1899.** 102.
38. Kumagawa u. Miura: Ueber Zuckerbild. aus Fett. im Tierkörper. D. A. **1898.** 431.
39. Arteaga: Phlorhizindiabetes in Cats. A. J. P. **6.** 173. 1901.
40. Zuntz u. Vogelius: Die Neubild. von Kohlehydraten im hung. Organismus. D. A. **1893.** 378.
41. Frentzel: Ueber Glykogenbild. im Tierkörper nach Fütterung mit Holzzucker. Ar. P. M. **56.** 372. 1894.

42. Nebelthau: Zur Glykogenbild. in der Leber. Z. B. **28.** 130. 1891.
43. Rolly: Ueber die Neubild. von Glykogen bei glykogenfreien und auf Karenz gesetzten Kaninchen. D. Ar. M. **83.** 107. 1905.
44. Spiro u. Hellin: Die Wirk. von Koffein und Phlorhizin bei artefic. Nephritis. E. A. **38.** 368. 1897.
45. Delamare: Glycosurie phlorhizique. Thèse de Par. **1899.**
46. Casper u. Richter: Ueber funkt. Nierendiagnostik. B. k. W. **1900.** 643.
47. Ellinger u. Seelig: Einfl. von Nierenveränderungen auf den Verlauf des Pankreasdiab. Festschr. f. Jaffé. 1901. 349.
48. Stiles and Lusk: On the Action of Phlorhizin. A. J. P. **10.** 67. 1903.
49. Grube: Formation of Glycogen in the Artificially Perfused Liver. J. P. **29.** 276. 1903.
50. Schmid: Fettsäuredarreichung Phlorhizindiabetes. E. A. **53.** 429. 1905.
51. Hartogh u. Schumm: Zuckerbildung aus Fett. E. A. **45.** 11. 1901.
52. Cremer: Entsteht aus Glyzerin und Fett im Körper höherer Tiere Traubenzucker? S. M. **1902.** Heft 2.
53. Lüthje: Zuckerbildung aus Glyzerin. D. Ar. M. **80.** 98. 1904.
54. Magnus-Levy: Vol. I.
55. von Noorden: Vol. II.
56. Embden, Salomon, Schmidt: Quellen des Azetons. Be. P. P. **8.** H. 3-4. 1906.
57. Mohr: Zuckerbildung aus Eiweiss. Z. e. P. **2.** 467. 1906.
58. Contejean: L'excrétion azotée dans le diabète de la phlorhizine. C. r. S. B. **47.** 344.
59. Lusk: Ueber Phlorhizindiabetes. Z. B. **42.** 31. 1901.
60. Mandel and Lusk: Respiration Experiments in Phloridzin Diabetes. A. J. P. **10.** 47. 1903.
61. Rubner: Die Gesetze des Energieverbrauchs. 1902.
62. Lusk and Stiles: On the Formation of Dextrose in Metabolism from the End-Products of a Pancreatic Digest of Meat. A. J. P. **9.** 380. 1903.
63. Rosenfeld: Die Fettleber beim Phlorhizindiabetes. Z. M. **28.** 1895; **36.** 1898.
64. Levene: Studies in Phlorizin Glycosuria. J. P. **17.** 259. 1894.
65. Schenck: Zuckergehalt des Blutes nach Blutentziehung. Ar. P. M. **57.** 553. 1894.
66. Bendix: Zuckerbildung nach Eiweissdarreichung. Z. P. C. **32.** 6. 479. 1901.
67. Bär: Untersuchungen über Azidose. E. A. **51.** 271. 1904; **54.** 153. 1906.
68. Geelmuyden: Untersuch. über Azetonkörper. Sk. Ar. P. **11.** 97. 1900.

CHAPTER XV

THE INFLUENCE OF LIGHT ON METABOLISM

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This section deals with the action of that radiant energy under whose influence we pass the greater part of our life, and which the retina is able to appreciate as light, rather than with the coarser effects and mechanical forces which affect the organism.

It has long been known that growth in the vegetable world is dependent upon light, and from analogy, as well as from the law of the conservation of energy, it is evident that the ether waves which penetrate the tissues —at least, so far as they are absorbed—result in other forms of energy, such as warmth, electrical phenomena, or chemical changes. These processes, which result in the animal body from irradiation, are but little understood, and our knowledge of them is less complete than that of the corresponding effects on plant life. That this is so can readily be understood, for the simpler the organization the more easily can the life processes be investigated. The development of complicated nervous and motor systems in animals must necessarily complicate the forces at work in them. Moreover, the simpler organisms are more amenable to physiological experimentation.

On these grounds it may be an advantage to cursorily consider the whole biological question, and to review in detail the response of some of the elementary organisms to the stimuli at present under discussion.

I.—THE PENETRATING POWER OF LIGHT.

A.—ORGANIC TISSUES.

In order to maintain that light produces effects in the body, it must be conceded that penetration occurs. No one will doubt but that light penetrates the outer layers of unicellular organisms; it is also certain that the cellular parts of the higher plants are so arranged that their extremities, such as the leaves, present sufficient surface to ensure an easy penetration of light.

The first investigation into the conditions obtaining in animals begins with Godneff (1), who placed capillary glass tubes charged with

chloride of silver under the skin of dogs and cats, and also under the prepuce in man, and found that blackening by light occurred.

Onimus (2) utilized a human hand of 26 to 30 millimetres thickness, and obtained a distinct impression on an orthochromatic plate with an exposure of five minutes.

Sarason and Darbois (3, 5), by means of concentrated light from a 50-ampère arc-lamp, produced blackening on a plate held in the mouth in one minute.

When Finsen (4) made the pinna of a human ear anæmic, and directed concentrated sunlight upon it, he obtained a photographic effect after twenty seconds ; but when blood flowed freely through that organ there was no effect, even after five minutes.

The most exact and comprehensive experiments were those of G. Busck (6). He produced results on an isochromatic plate in ten seconds with concentrated sunlight through a hand though the weather was not bright.

The concentrated light of a carbon arc-lamp of 70 ampères and 50 volts acted through the middle of the hand (2·8 centimetres) in one second, but was much slower in other parts — *e.g.*, the wrist-joint (3·7 centimetres) in four minutes. As he obtained uniformly negative results with the most sensitive plates in trying to pass light through the forearm (5·6 centimetres), Busck concluded that it was useless to look for translucency through denser parts of the body. Yet light can be seen through considerable thickness of tissue—as, for instance, in transillumination of the stomach.

All investigators who have considered this question are now in agreement that only the red-yellow light rays have any great penetrating power, and that the blue-violet rays do not reach the deep parts at all.

Finsen, who also paid attention to this point, had already shown, in 1899, that the short-waved rays penetrate further into anæmic than into blood-containing tissues. Even with very thin membranes a high absorption takes place. This was confirmed by Drossbach (7) for fowls, and Freund (8) for the blebs of burns and pemphigus.

Further knowledge on this point is gained from researches on the bactericidal power of light, for the most extreme ultra-violet rays are the strongest in bactericidal power. Jansen (9) maintained the opinion that concentrated electric light exercises a bactericidal power up to a depth of 1½ millimetres of anæmic skin, and an inhibitory action upon growth up to 4 millimetres. This power appeared to be due to the inner ultra-violet rays of 406 to 322 millimetres, and to the blue-violet rays ; the outer ultra-violet rays had been absorbed under the conditions of the experiment.

Busck (10), who worked with ears of rabbits not rendered anæmic, came to the following similar conclusions : The curve of the penetrating power of the various kinds of rays starts from the most extreme ultra-violet, where the penetrating power is peculiarly small, and passes through the inner ultra-violet and the coloured part of the spectrum ; the rise continues to somewhere in the ultra-red end, where, accordingly,

the maximum for the penetrating power exists. In the outer part of the ultra-red the curve drops again.

About 22 per cent. of the red-yellow rays pass through the congested rabbit's ear, about 16 per cent. of the white light of an incandescent lamp, but only about 1 per cent. of the blue-violet, and none of the ultra-violet.

The importance of these investigations permit extensive conclusions to be drawn. In the first place, there is no absolute necessity that a force must penetrate deep into the tissues in order to exert its influence. Indeed, the chemical rays exert a marked influence on the skin through which they pass (11). Although we have reason to ascribe to the short wave-length rays a marked influence on the metabolism of the tissues, we must not deny to the red-yellow rays any action merely because we are as yet ignorant of the means by which they play an important part in the life of plants.

B.—CLOTHING.

Boubnoff (12) concludes from his investigations upon the penetrability of human clothing for light that the animal and vegetable substances which are used for clothing are permeable to the chemically acting rays of sunlight. Uncoloured materials are more easily permeated than coloured ones. Black cloths are, *cæteris paribus*, less permeable than others. The transmissibility of the chemical rays depends mainly upon the colour and thickness of the material, and seems to vary very little with the source of the chemical rays. It is the same whether the rays are derived from diffused daylight or from the sun (13).

As far as man is concerned, however, the influence of the clothes must not be rated too highly, the blood-stream in the uncovered parts of the body is constantly subjected to the influence of the light, and then courses to other parts of the body.

II.—THE INFLUENCE OF LIGHT ON DEVELOPMENT, PROPAGATION, AND CELL LIFE.

A.—BACTERIA.

The best outline of our knowledge on the influence of light on bacteria was published in the year 1878 by Downes and Blunt (14).

It is generally agreed that light (sunlight, diffused daylight, electric light) exerts a harmful action upon bacteria, in proportion to its intensity of producing arrest of development, lessening their virulence, or producing death (15). This inimical influence is derived especially from the most refrangible rays of the spectrum, but also from others.

Of further biological interest was Roux's discovery that in bouillon exposed for more than an hour to light anthrax spores would not

germinate, although the organism itself could still be grown on fresh culture medium. The question assumed a more important form when Richardson (15) showed in 1893 that on raying urine peroxide of hydrogen was developed—a material to which he attributued the bactericidal power of light—and these experiments were confirmed in principle by Dieudonné and Kruse. Bie showed that peroxide of hydrogen was only produced when the fluids contained organic nitrogenous compounds, but that the bactericidal power of light appeared also in quite indifferent media, such as in distilled water.

We have, therefore, to admit a direct influence on the protoplasm of the micro-organisms—a fact which is not incompatible with the formation in the culture medium of a bactericidal substance, hydrogen peroxide in particular.

A second important biological question is whether the bactericidal power of light is connected with the formation of oxygen, a question which in their time was answered by Downes and Blunt in the affirmative. As here laid down by Bie, the matter amounts to this: that the presence of oxygen is not essential to the bactericidal power of light, but is advantageous, and that this advantage shows a relation to the extent of chemical rays present in the particular light employed.

Bacteria can be killed in the living tissues, in certain circumstances, by light, in spite of the rapid absorption of the greatest part of the ultra-violet rays in the superficial layers of tissue $\frac{2}{10}$ to $\frac{3}{10}$ millimetre thick—by the blue-violet and those ultra-violet rays which lie next to these [Böder, Jansen, Nagelschmidt, Busck (16)].

In practical phototherapy a certain part of the curative effect may depend on the bactericidal power of the light rays, but the greater part is due to the hyperæmia and inflammatory reaction of the skin.

B.—PROTOZOA.

There are only a few statements on the multiplication and growth of unicellular organisms in light or darkness, partly because the determination is more difficult than in the case of bacteria in pure culture, and partly because their biological importance brings them nearer to man. Schmarda (16) asserts that light of little intensity exerts a favourable influence on infusoria, and Serrano Fatigati (16) states that violet light has a favourable influence on development. But it must probably be maintained that somewhat concentrated light will exert a weakening and destroying effect on the delicate organization of the protozoa in the same way as on bacteria.

For animal cells this, amongst other things, becomes plain from the investigations of Busck (16) on the destruction of ciliary epithelium by light. Jensen and Jansen (17) have made it clearer still by destroying with concentrated light the cells of a tumour in a mouse, and causing the disappearance of the tumour. The cells of the human skin are more resistant, since in the Finsen treatment necrosis does not generally occur [Busck].

C.—HIGHER ORGANISMS.

It appears somewhat contradictory that this force, which arrests development and exerts an adverse influence on the lowliest organisms, should appear to favour the development of more organized forms of life. In the experiments on the lower organisms, however, the concentration of light was relatively higher than that which exists naturally, and the action was more localized. When subjected to light rays of greater intensity, higher animals are also deleteriously affected.

1. Plants.

The importance of light for plant life is shown particularly in two directions: Firstly, chlorophyl is not formed in the dark; secondly, darkness favours development of a plant, while the growth is an abnormal one. Then, like the formation of chlorophyl, the production of wood and of the cuticle of the cell membrane (*étiolement*) are suppressed.

Simultaneously with its action on development, light also exerts an influence on the direction of growth of the plant (positive and negative heliotropismus)—a process by which in some there is produced an acceleration in the growth of the side turned away from the light, and in others an influence on the tension of the tissues.

In the lower animals also there are processes quite similar to those in plants (positive and negative heliotropic direction development) [Jacques Loeb (18)], which correspond to the osmotic processes at the internodes —viz., the alterations in the tension of the musculature.

2. Animals.

(*a*) *Development.*

In 1824 Edwards (19) established the fact that light favoured the development of tadpoles from frogs' spawn, and that in darkness only poor specimens developed. Since then there have been a series of investigations, with negative results, however, in the frog and lizard (20, 21). Schnetzler (22) attributes this to imperfection in the experimental conditions. His tadpoles also were retarded in the dark, as were the fly larvæ of Godneff (1). Young (23) obtained similar results with the eggs of *Rana*, *Salmo*, and *Lymnea stagnatis*.

Violet light hastens development in a marked degree; blue, yellow, and, lastly, white light, and red and green rays are directly prejudicial, and darkness at least retards. With the eggs of flies, and in worms under violet and blue bell-glasses—in contradistinction to red, yellow, white, or green—Béclard found the general processes accelerated (24). Féré (24) has shown the superiority of white light as opposed to orange or violet for hens' eggs. Only Davison and H. Driesch (24) came to completely

opposite results, the former with the eggs of *Musca vomitoria* and the latter with *Rana echinus* and *planorbis*. They consider that white light delays development and blue is directly prejudicial.

In reviewing these researches, it must be observed that the conditions of the experiments are often unsatisfactorily specified, and often lacking altogether. The absorption of the glasses used has not been tested spectroscopically; and in the researches in the dark, often the deficient ventilation of the experimental chambers has not received sufficient attention. The most detailed and trustworthy investigations are those by Schnetzler and Young which yielded the positive results already alluded to.

The experiments on mammals are even less reliable. The details of input and output are omitted.

Hammond (25) and Gorbatzewitsch (26) state that kittens and puppies develop better in light. Pleasanton (27) considers that violet light favourably influences the growth of pigs. Loeb writes: "Pleasanton's book is printed in blue letters, and gives for all the natural phenomena of life up to the activity of a volcano what might be termed a blue interpretation."

Borissow (63) showed that puppies and young rabbits, when kept in a darkened room, always had less appetite than controls living in the light, and were correspondingly deficient in body-weight. This accords with the well-known fact that light stimulates movement, and thereby increases nutrition. When geese and fowls are kept in narrow, dark cages, it is not so much the lack of light as the need of exercise which results in the deposition of fat, quite apart from the forced feeding. The more rapid consumption of food by wild animals has often been attributed to light [Bidder and Schmidt, Adducco (28)], although it naturally depends upon a greater use of the muscles.

(*b*) *Organ Formation.*

Jacques Loeb, who, moreover, did not consider that any influence of light on general development had been proved, showed that in *Endendrium racemosum* polyp formation occurred only in light, while in the dark there was only the formation of tentacles. Only the blue rays had this effect, the red acting in the same way as darkness. Milroy (143) has investigated the response of the developing retina of the chick to light. He finds that the cells first respond to the light on the fifteenth day, and the response becomes more intense as development proceeds. Light has no effect on the development generally.

III.—INFLUENCE ON MOTOR PROCESSES.

Light exerts a stimulating effect on the motor systems of the lower as well as of the higher organisms.

A.—BACTERIA, PLANT CELLS, AND PROTOZOA.

The *Bacterium photometricum* moves only in light, and groups itself under the rays of greatest intensity [Engelmann (29)]. Similar phenomena are met with in many of the lower plants and animal forms, in the wandering spores of *Botrydium granulatum*, in the *Plasmodium* of *Æthalium*, and in the wandering spores of *Volvox globator* [Strassburger (30)]. It is in this way that what is known as phototaxic processes vary in their different forms of positive or negative phototaxy, according to the intensity of the light and other extraneous conditions. The kind of light also makes some difference. *Paramœcium cussaria* group together at the red, while *Englena viridis* does so in the blue, part of the spectrum [Engelmann].

Although in part these phenomena may be produced by the indirect effects of light in a roundabout way by the influence of the production of oxygen and other extraneous conditions, yet they are mainly due to the direct influence of light [Engelmann].

Many motor processes lead to no change in the position of the cells, but are expended in the protoplasm itself, the protoplasm contracting with sudden exposure to light, amœboid movement increasing or being arrested (phototonus, light contraction).

B.—METAZOA.

The process becomes more complicated as we ascend the animal scale and meet with associated nerve centres. It is not known how much of the motor stimulus is dependent on the excitement of the cell itself, and how much on the influence of the nerve apparatus. But we must recognise the fact that the stimulating power of light is everywhere established. Bert (31) describes how a frog, even when blind, moves towards the brighter part of its cage. The avoidance of light by blind worms observed by Graber (32), the similar researches by Dubois (33) in *Proteus anguineus*, and Finsen's (34) careful experiments on salamanders, which, even inside the eggs, were most lively in white and violet light, all demonstrate this stimulating character of light. For the varying actions of the individual colours of the spectrum, see Finsen (34).

The effect of light on movement in higher animals and man can more easily be suggested than proved. It agrees with the varied

experience of daily life (35). On the other hand, there are certain researches which attribute to the blue rays a sedative, and to the red rays a stimulating, effect. Such have been observed in psychology, but the matter is still somewhat problematical.

Apart from direct motor influence, the continuous influence of light is responsible for the muscle tone (18, 39). As an example from human pathology, Romberg's phenomenon may be cited—viz., the swaying of a tabetic when his eyes are closed. We must agree with Loeb, however, that this phenomenon is not entirely explained by the momentary cutting off of the sense of vision.

IV.—THE EFFECT OF LIGHT ON OXIDATION.

In so far as light serves as an incentive to movement for the organism, its effect in increasing oxidation becomes clearer when we appreciate that each act of movement demands the combustion of organic material. Whether besides this more indirect effect there is still a direct influence of light on the power of oxidation in the cells themselves is an important question, but one which cannot be easily answered. The association of these motor processes which are connected with the increased consumption of oxygen renders the matter so exceedingly complicated that observations which were apparently definite are met by the critics with the question, " Were all such movements excluded ?"

A.—IN PLANTS.

The movements of the higher plants are quite separate from this consideration. However, a certain power of light in hastening oxidation can with difficulty be observed in them. If there is also in the animal body a combustion process corresponding to that in plants, then during the day the reverse process of the assimilation of CO_2 takes place—a process which that material called leaf-green (chlorophyl) brings about under the influence of light, and certainly of the visible part of the spectrum. As by these processes oxygen is set free, one cannot distinguish clearly between the phenomena of assimilation and the respiration of plants in light. This is certainly one of the reasons why the power of light in increasing oxidation is considered essential to the animal body.

B.—IN ANIMALS.

1. Cells and Isolated Tissues.

On account of the difficulties in technique, the analysis of the interchange of gases under these conditions has not yet been carried out in the case of isolated animal cells. Yet Quincke (35) has sought to show

that oxidation in animal cells is hastened by light. He mixed pus with blood or with a watery suspension of subnitrate of bismuth. The hæmoglobin band disappeared, or the bismuth subnitrate blackened more rapidly in light than in the dark.

The phenomenon, as Quincke himself has shown, occurs also if yolks of eggs, fresh butter, etc., are used, and also, though to a less extent, with cooked organs.

It cannot, however, be certain that there is a proof in these phenomena that any surviving cells remain, and the phenomenon brings to mind the process of " sensitizing."

Surviving muscle and nerve tissues (brain and spinal cord), according to Moleschott and Fubini (37), respire more freely in the light than in the dark. The difference is very marked—141 to 100 for dog's muscle, 149 to 100 for dog's brain. These researches were openly characterized by J. Loeb (48) as researches on dying and dead tissues, and to be explained by the onset of decomposition. That the respiration of nerve tissue should reach as high a value as the authors maintain—*e.g.*, 0·527 gramme CO_2 in twenty-four hours from 100 grammes of guinea-pig's brain in the light, and 0·387 gramme in the dark—figures which would be quite compatible with muscle tissue—must also be a mistake. Also, the researches of Tissot and Fletcher sustain the view that the CO_2 given off by surviving muscle springs from no definite source. Further investigations are much wanted.

2. Animals.

(*a*) *The Consumption of Oxygen and the CO_2 Output by the Lungs.*

Since Moleschott showed, in 1855, that frogs expired from one-twelfth to one-quarter more carbon dioxide in light than in the dark, that the excretion of carbon dioxide increased with the intensity of the light, and that the effect of the light indicated was produced partly through the eyes and partly through the skin, and since Pflüger (39) drew fresh attention to the great biological importance of the matter, a considerable amount of work has been carried out on these lines. From early times much attention was paid to the study of a specific effect of light on the respiration of the cells (37), while no regard was paid to the increase of movement due to light in the animals under observation. But even where this has been done a definite verdict is not forthcoming, and each single experiment in this direction avoids with difficulty the mistakes of its predecessors, only to fall a victim to a later critic (38, 43).

Moleschott and Fubini (37) considerably extended their observations in 1882 on frogs after extirpation of the eyes, brain, and cord, and after removal of the skin. One such frog yielded CO_2 per hour :

Date.	*In Dark.*	*In Light.*	*In Dark.*
November 4	0·0056	0·0037	0·0027
,, 6	0·0028	0·0080	0·0072

It may be noticed that the first value of the early period in the dark on November 4 is in excess of the following period in the light. Such contradictory conclusions are frequently met with in these researches. A large number of individual observations are made, and single mistakes are compensated for by the mean of a long sequence.

A. von Platen (39) observed in Pflüger's laboratory that rabbits which were similarly fastened down gave an average of oxygen consumption in the proportion of 116 : 100, and of CO_2 production of 114 : 100, according as to whether the eyes of the animals were exposed to, or shut off from, light. Speck (42), however, maintained rightly that in these experiments the influence of muscle movement was not excluded.

The experiments made by Fubini and Benedicenti (40) on hibernating animals such as dormice and bats are not numerous, but appear to us to be proportionally conclusive. Although Jaquet's figures evidence irregular results, and in connection with the gaseous interchange a factor which cannot be precisely determined is apparently present, yet it is impossible to feel otherwise than that there is some definite principle underlying the matter. For instance, the following figures from an experiment on *Myoxus glis* (E.) suggest that some unknown factor was at work on January 2 (dark) :

Date.	*CO_2 from 100 Grammes of Animal in Twenty-four Hours.*	
	Light.	Dark.
December 19	1·5930	1·2830
,, 20	1·9595	1·8017
,, 23	1·1023	0·7299
,, 24	1·7052	0·9852
January 2	1·5119	0·1350
,, 3	1·0017	0·5830

Speck (42) obtained a similar result when he examined himself, sitting in a chair with eyes open and closed. There occurred in the light a slight increase of frequency and depth of respiration, which produced an increase of oxygen consumption in the proportion of 100 : 101, and the excretion of CO_2 in the proportion of 100 : 104. Therefore the change was merely in the mechanical conditions of respiration.

Criticism upon Speck's work suggests that an experiment on himself might be accompanied by unconscious contraction of muscle—perhaps in the dark—and that the duration of the experiment (nine to thirteen minutes) was too short.

Loeb arrived at opposite conclusions from an investigation upon the loss of weight and interchange of gases in light and darkness in chrysalides, though how much light penetrated the dark chitinous shells ought to be previously determined ; the amount could scarcely be large.

Ewald found that in curarized frogs the CO_2 output only varied about 5 per cent. in light and dark. This did not evidence a recognisable

influence of the light, nor avoid the objection that, owing to the curare, an unknown factor had been introduced into the economy.

Salomon observed that the light of an arc-lamp of 10 ampères and 800 candle-power at 1½ millimetres distance gave the following figures :

	Oxygen Consumed per Minute.	*CO_2 Expired per Minute.*	*Respiratory Quotient.*
Previous experiment in diffused daylight	249·8	187·3	0·749
Experiment with electric light playing on trunk and thighs for twenty-three minutes	249·7	196·2	0·785
After experiment	233·2	164·5	0·705

It is evident that no definite effect was produced.

So we are compelled to state that this influence of light on the oxidation energy of the body has never yet been certainly determined, although such action cannot be definitely excluded. For many reasons the question reminds us that the increase of oxidation due to external cooling depends entirely upon whether this increased oxidation is independent of or dependent on the shivering. If we admit the reflex effect of light on the innervation of muscles supposed by Pflüger, Loeb, and others, we ought, therefore, to expect an effect on the consumption of oxygen.

(*b*) *Skin Perspiration.*

The CO_2 loss through the skin is, according to Fubini and Ronchi (45), more rapid in the light than in the dark in the proportion of 113 : 100.

(*c*) *The Effect of Definite Spectrum Colours on the Interchange of Gases.*

The statements of Pott and Piacentini, of Fubini and Moleschott (37), differ, according to the species of animal employed, and also from one another, to such a degree that no definite action can be deduced in any way ; still less so as the free movements of the animals vitiated the experiments.

(*d*) *The Influence of Sunshine.*

All the experiments mentioned hitherto have sought to determine the influence of light apart from warmth, namely, by observations in diffused daylight, and after absorption of heat rays by means of a layer of water, in order to obtain similar and uncomplicated conditions for light and darkness. In direct sunlight the conditions are altered.

Direct sunshine saves the total amount of necessary heat production in dogs—as, for instance, when the heat ray leads to a higher tempera-

ture of the air, a temperature not incompatible with the details of ordinary chemical regulation of heat, and when the animal is thereby compelled to perform increased respiratory work (46).

The rapid respiration of dogs when overheated does not occur in man, in whom the action of the sweat glands comes into play.

As for the rest, the effect of the sun on the interchange of gases, which is quite the same in dogs as in man, shows that the gaseous interchange is so arranged for any temperature as if the latter were equal to the prevailing air temperature plus half the difference of the sun and shade temperatures ; so that the heat regulation of an animal at a shade temperature of 20° C. and a sun temperature of 38° C. would be so managed as if the air temperature were raised from 20° to 29° C. [Wolpert (47)].

The results obtained by Wolpert with naked and dressed men [Zuntz, Geppert's method] are as follows :

	Remarks.	*Temperature in Shade.*	*Temperature in Sun.*	*Amount breathed per Minute.*	*Oxygen Consumption per Minute.*	*CO_2 produced per Minute.*	*Respiratory Quotient.*
1. Mean of six observations	Clothed in shade	20·5° C.	—	4·949	292·0	211·7	0·73
2. Mean of two observations	Clothed in sun	22·0° C.	38·0	6·376	336·0	212·4	0·67
3. One observation	Naked in shade	25·0° C.	—	6·052	318·3	208·8	0·66
4. Mean of two observations	Naked in sun	29·7° C.	40·7	5·480	307·7	187·8	0·61

The perceptible increase in the breathing volume in Experiment 2 (and a consequent increase in the corresponding oxygen consumption) is, according to Wolpert, in agreement with the increased ventilation of the skin which the clothes produce, for the depth of respiration is increased in a perspiring person.

These experiments, also, carried out as they are with muscles completely at rest, do not reveal any considerable appreciable increase in consumption of oxygen through the action of light.

Therapeutic Considerations.

The action of light on metabolism in man is only slight. If, however, light is not itself the agent, as far as any practical application is concerned, the known procedures are associated with not inconsiderable changes in the economy.

(*a*) *Sun Baths.*

Exposure to the sun does not increase the processes of combustion (47). Wolpert carried out experiments upon this point in a photographic studio protected from any draught, the roof and outer wall being com-

posed of glass. A sun bath is for all practical purposes a sun-air bath, there being a certain amount of draught in addition to the sun's rays. This may easily be recognised from Wolpert's work (48). Only in lower temperatures, when cooling takes place at the same time, is it a matter of considerable importance to the extent of the process of combustion, an increase taking place under that condition.

Sun baths are generally given in the following manner: The whole surface of the patient's body is exposed for half to one hour to the rays of the sun, and is then well wrapped up in blankets. Secretion of sweat ensues, and the body temperature rises. The effect of a sweat bath is produced, and a moderate increase in combustion takes place. Finally, the patient is massaged and then given a cold bath or packing—that is, with cold and mechanical irritation.

A series of influences partly affect the estimation of the total effect, which are dealt with in another place [*cf.* Matthes, The Influence of Baths on Metabolism].

(*b*) *Incandescent-Light Baths.*

An incandescent-light bath—as the lamps give out almost entirely heat rays and only very few chemical rays—produces a similar effect on oxygen consumption and CO_2 production to that of Quincke's hot-air bath; the extent of respiration is deepened (49).

Sweat appears earlier, perhaps, owing to a direct effect of the rays on the sweat glands [Krebs (50)]. Any increase of the oxidation which occurs in the incandescent bath must not be estimated too highly. The increase of the consumption of oxygen in a brilliant incandescent-light bath of about two and a half hours' duration (7 litres oxygen), if measured in fat combustion, only corresponds to about $3\frac{1}{2}$ grammes of fat.

The effect on the water economy is naturally of importance, as the loss of sweat reaches 2 litres or more. A corresponding change in the concentration of the blood and blood-serum occurs, dependent upon the systematic use of the bath and the lessening of the systemic fluids.

With this there is a progressive increase in the amount of hæmoglobin and the number of the red blood cells. The somewhat contradictory statements on the latter observations (51), in which individual differences in the extent and rapidity of the sweat production obviously play a part, are admirably reviewed by Krebs and Mayer (52). It is not actually a new condition, but only a result of the thickening of the blood and the altered conditions of the circulation. Probably it is on all-fours with the increase in the neutrophilous polynuclear leucocytes (52). Perhaps thermotactic influences come into play also.

An increased excretion of nitrogen is probable (53). Further investigations are required upon this point.

(c) *Arc-Light Baths.*

It is to these that we must first look for any peculiar effect of light on metabolism. But, then, the light of an arc-lamp is especially rich in chemical and physiological blue-violet and ultra-violet rays—richer than sunlight, the ultra-violet part of which is considerably absorbed in the atmosphere.

Here, however, the effects of heat are the only ones known, and as far as sweat production is concerned, they are less effective than incandescent-light baths. The rectal temperature may be raised by 4° to 6° C. [Hasselbalch (54)].

Although the gaseous interchange is but slightly altered by arc-lamp baths, deepened respiration with diminished frequency may follow for a whole day afterwards [Salomon, Hasselbalch].

The therapeutic value of an arc-light bath is minimized by the fact that its use must be restricted when erythema is produced.

V.—THE EFFECT OF LIGHT ON ENZYMES.

Light appears to diminish the action of a number of enzymes. Downes and Blunt (14) found that sunlight destroys invertins. The diastasic ferment in the leaves of plants is, according to Green (55), destroyed by the ultra-violet rays. Emmerling and Weiss (56) record negative results. In many instances, however, in experiments with glass apparatus, the active ultra-violet rays are cut off by absorption. In the experiments of Schmidt-Nielsen (57), to which no exception can be taken, the insertion of a piece of colourless glass was sufficient to prevent this action on chymosin.

The destructive effect of light on bacterial toxins has often been established.

For the sensitizing of toxines and enzymes, see Sensitization.

VI.—THE EFFECT OF LIGHT ON THE BLOOD.

From the action of light in the production of chlorophyl and the close chemical relations of chlorophyl and hæmoglobin, and from the marked absorption of the ultra-violet rays by hæmoglobin, it is fair to suppose that light is able to act upon the constituents of the blood.

A third fact may be added : Von Schläpfer (58) proved that blood exerted a definite effect upon a photographic plate after the blood had been exposed to the sunlight. The effect was intensified when larger quantities of blood were employed. When albino rabbits were used, the result was more marked than with those ordinarily pigmented. He

suggested that the blood might be able to store the light rays which were received on the surface of the body in the vessels of the skin, and give them up again inside the body.

Practically nothing is known as to the precise action of light on the blood. We hear of children who have been brought up in the sunless streets and courts of great cities having to go into the country on account of pallor and rickets ; but it is apparent that they are the results of a medley of unhygienic factors, and not only of the absence of sunlight.

A.—ACUTE EFFECTS.

Fülles (59) observed an acute effect of light on the blood when an animal was removed from darkness into light. An instantaneous raising of the specific gravity occurred—*e.g.*, from 1047 to 1050. This difference, moreover, continued throughout the whole day. It probably arose from a vasomotor irritation, resulting in a different distribution of the blood in the vascular organs.

Linser and Helber (113) examined the blood 15 to 100 hours after irradiation with an arc-lamp, but were not able to observe any definite effects.

B.—CHRONIC EFFECTS.

The results obtained vary considerably. With regard to animals, Marti (60) found the number of erythrocytes diminished in the dark, while they increased in sunlight and electric light, as also under the influence of other irritations of the skin.

Graffenberger (61) noted similar results in the hæmoglobin of rabbits kept in the dark. Darkness for a longer time lessens the total quantity of the blood. It will be understood that weighing the quantity of blood allowed to drain out does not give us the most definite quantity of blood that it is possible to obtain.

Schönenberger (62) recorded quite opposite effects—viz., increase in the erythrocytes and concentration of serum and hæmoglobin—but in his experiments the control animal showed a considerable tendency in the same direction as the animals experimented upon.

Borissow (63), in apparently careful experiments, did not find any effect of light on erythrocytes and hæmoglobin.

Under such abnormal conditions as absolute darkness, it is probable that after a certain time a fall in the cells and hæmoglobin should occur in the blood because of the often unavoidable influences of the experimental conditions upon the general state, appetite, movements, etc. No direct influence, however, appears to be constantly present in every case.

It is a somewhat indicative fact that those who take part in polar expeditions are wont to show a pallor bordering on a yellow-green colora-

tion of the skin. Gyllenkreutz (64) examined the blood, and found an impoverishment both spectroscopically and morphologically.

It is very possible, according to the findings of Finsen, that this depends upon the absence of the vaso-dilating property of light [Bie]—that is, on a chronic " capillary anæmia."

VII.—PROTEIN METABOLISM.

The albumin metabolism was found by Graffenberger (61) to be exactly the same for two rabbits, one of which was kept in a light and the other in a dark hutch for a preliminary period of forty-six days and a subsequent observation period of eleven days' duration. With an entire supply of nitrogen of 17·2 grammes the one in light retained 2·8 grammes, the other 2·5 grammes, for the whole period of examination.

VIII.—INTESTINAL DIGESTION AND FOOD ABSORPTION.

There are several statements in Graffenberger's work, but it is not shown that there exists any substantial difference between animals kept in the light and those in the dark. Statements of disturbance of intestinal activity in the dark are not to be wondered at, as generally there are depressing influences at work on the activity of the intestinal canal.

IX.—EFFECT OF LIGHT ON THE SKIN.

A.—IN ANIMALS.

Many lower animals change the colour of their skins according to the illumination, the pigmentation of frogs, cuttle-fish, and chameleons, and that of others, becoming paler in light [Jensen (65)]. The higher animals are more darkly coloured as a rule on those parts which are most exposed to the light—*e.g.*, the back.

B.—IN MEN.

In man, the intense effect that light has upon the skin in certain conditions has long been attributed to the effect of heat. Inflammatory conditions occur, however, under the action of electric light when the skin is not warmed [Malakoff (66)], and some patients exhibit an idiosyncrasy to sunlight who are not affected by the otherwise stronger heat rays from hot ovens, etc. [Veiel (67), Hammer (68)].

The kind of inflammation of the skin also differs from the peculiar symptoms after heat, and the erythema caused by light, though morphologically similar to that caused by heat, leaves behind a still perceptible pigmentation when the inflammatory changes have entirely subsided.

Widmark's (69) researches on the absorptive selection of the individual parts of the spectrum indicate that the chief effect is produced by the ultra-violet rays. In further proof of this point, Finsen (70) showed that by covering the skin with uncoloured glass (which absorbs ultra-violet rays to a high degree) the development of erythema may be prevented—a fact which has led to the use of rock-crystal lenses in the Finsen treatment.

Finsen also showed that the blue and violet rays have an irritative effect on the skin, though to a less degree.

Pigmentation resulting from light erythema is a protection to a marked degree against further dermatitis [Finsen (70)]. It is not a far cry teleologically to the property of the cutaneous pigment in negroes.

Light erythema has all the anatomical characters of an inflammatory hyperæmia of the vessels, such as diapedesis of white corpuscles, etc. [Dreyer and Jansen (71)]; yet months afterwards, when the colour of the inflamed skin has become the same as the intact skin, a marked reddening of the previously erythematous part may be induced by friction [Finsen (70)]. Hypersensibility of the cutaneous vessels is, therefore, a frequent sequela.

The irritative action of the blue-violet and ultra-violet rays was so intense that it led Finsen (72) to return to the old empirical method of treating small-pox in the dark or in red light. Although there is no influence on the course of the disease, this treatment—and on this all investigators agree—hinders the development of the pustules, and so influences favourably the formation of the scars.

X.—SENSITIZATION.

Hitherto the phenomena described have had to do with a variable factor which can be decomposed into its several spectrum bands. Recently, however, a way has been discovered by which the penetrating powers of light may be increased. This is brought about by a process of sensitization.

A.—SINGLE CELLS.

Raab (74) noticed that the poisonous qualities of solutions of akridin, eosin, and phophin for infusoria were increased a thousand times by allowing them to act in the presence of light. Since that time there have been a series of chemical bodies denominated having similar properties. They all have the property of fluorescence in common (74).

The effect extends to animal cells in general, to ciliary motion [Jakobsohn], and to bacteria [G. Dreyer (75)]. Saccharoff and Sachs (76) showed that the active principle in light possesses hæmolytic properties.

B.—TISSUES.

Raab (74) had already found that sunlight produced a local necrosis in the ears of mice which had been injected with eosin. Jakobsohn (74) showed that frogs suffered from paraplegic symptoms as the result of the same subcutaneous dose of eosin in light which they could tolerate quite easily in the dark. Dreyer noticed the appearance of œdema, injection of the vessels, and thrombosis of the capillaries in the different tissues containing eosin under the influence of light (frogs' tongues, rabbits' ears) (75).

C.—ENZYMES, TOXINES, ETC.

On account of the great importance in biology of those substances allied to enzymes, the latter were immediately brought into the domain of radiation, and analogous effects established. When papayotin, diastase, and invertin were mixed with eosin or Magdala red and rayed, their activities were considerably weakened [Tappeiner (77)], just as also were toxines, ricin, tetanus toxine, diphtheria toxine [Tappeiner and) Jodlbauer (78)], as well as the complements of serum (von Lichtwitz (79].

The weakening of the diphtheria toxine is also noticeable in animals, in that those previously treated with eosin or methylene-blue tolerate an ordinary lethal dose.

D.—THEORY.

Raab has already performed instructive experiments on the production of the dynamic effect of light, the most important of which are here included.

Paramæcia survive for a longer time in light which has previously passed through a solution of akridin. It cannot, therefore, be due to an alteration of light alone.

For the majority of chemical poisons paramæcia are no more sensitive in light than in the dark. Light in itself does not tend to kill the paramæcia.

As akridin solution has neither any effect on the light, nor light any on the paramæcia, there must be a change produced in the akridin solution. This effect is dependent upon the direct presence of light, for the solutions of akridin, eosin, erythrosin, etc., were previously exposed to light, and their effects upon paramæcia examined in the dark, and no peculiar toxic effect was found.

It is certain that an absorption of light plays a part in the change of the photodynamic material. It must be expected, and understood from what has been already cited, that light which has previously passed through a layer of akridin solution has a considerably weaker—certainly not an increased—photodynamic effect on a paramæcium-akridin suspension [Raab]. The fluorescence of the photodynamic material plays also an important part. This has never yet been missing in any case

[Tappeiner, Tappeiner and Jodlbauer (80)]. Accordingly, the "sensitizing" effect is the greater the less the brightness of the fluorescence of the photodynamic material, unless certain proportions are attained [Tappeiner and Jodlbauer (80)]. This corresponds with the following facts.

It is not the fluorescence emitted which is the effective agent in the phenomena, for paramæcia cultures, enzymes, etc., can be rayed on all sides with the fluorescence of the photodynamic material—as, for instance, through a small test-tube inserted into a larger one filled with a layer of fluorescent material—without any result occurring [Raab].

The physical nature of the fluorescent phenomena is not yet clear. It is only possible to consider, on general grounds, that the fluorescing body can change the radiant energy into chemical energy. Ionization, apparently, plays a part in the process.

The photodynamic effects described have a more complete similarity with the process of sensitizing photographic plates. Vogel discovered, in 1873, that bromide of silver plates, which are usually only sensitive to chemical rays, in the presence of certain colours become more affected by the less refrangible rays, and especially by those which the added colour has absorbed (orthochromatic plates). There is no satisfactory explanation of this process. The great resemblance of this optical sensitization with photodynamic effects has been often referred to (73, 75, 81). Yet it appears that there is no identity of the two processes, for the best optical sensitizing agents work without any photodynamic effect at all, and *vice versa*. The most active photodynamic materials do not sensitize photographic plates [Tappeiner and Jodlbauer (80)]. There may exist some important connection between these processes after all.

E.—THE IMPORTANCE OF THE PRESENCE OF OXYGEN.

Ledoux-Lebard (82) observed that the presence of large quantities of oxygen favours the effect of the fluorescent material. Further work has directly shown that the presence of oxygen is an integral factor in the production of the photodynamic reaction—*i.e.*, that it depends upon the living cells or the dissociation of iodine from potassium iodide [Straub], or upon the oxidation of β-naphthol to form β-naphthol-chinone [Edlefsen]—processes which, like the deleterious effect on cells, enzymes, and toxines, are favoured in the light by the addition of a fluorescent substance (76, 83).

Nevertheless, there are also chemical reactions which are hastened by light and fluorescence when oxygen is excluded, and which are arrested by light and fluorescence in the presence of oxygen—*e.g.*:

$$2HgCl_2 + 2(NH_4)C_2O_2 = Hg_2Cl_2 + 2NH_4Cl + 2\ CO_2$$

[Jodlbauer and Tappeiner (83)].

The principle that the presence of oxygen is necessary for photodynamic action is not proved, in spite of it being the rule in nearly all the cases in point.

F.—THE GENERAL BIOLOGICAL IMPORTANCE OF SENSITIZATION.

The distribution of fluorescent substances is so wide in the animal and vegetable kingdoms that many of the phenomena of life present an opportunity of comparing photographic and photodynamic sensitization.

One fluorescent colouring material of the greatest importance for the assimilation of CO_2 by plants is chlorophyl. The change of radiant into chemical energy which takes place in a leaf may be compared to the importance of the coloured sensitizer for photographic plates. A similar phenomenon occurs in the action of the equally fluorescent visual purple [G. Busck (16)].

Blood-serum also fluoresces, so that it is quite possible that photodynamic processes take place inside the body, even if they are not of an extensive character.

G.—EXAMPLES FROM PATHOLOGICAL CONDITIONS.

That certain processes of a photo-dynamic nature have been experimentally produced in pathological processes is well known. Of special interest is the spontaneous appearance in cattle of what is known as the *Buchweizen* disease.

Wedding (84), in 1887, directed attention to the fact that in cattle and sheep fattened on buckwheat a vesicular erythema developed when the animals were in light, whether sunlight or diffused daylight. Tarring of the skin hindered the development of the affection, and the spots covered with black hair were not affected. Virchow (84) confirmed these observations.

According to Busck, the buckwheat contains a fluorescent material —" fluorophyll "—and if his clear demonstration has not sufficiently succeeded in proving the question experimentally, yet it is apparent that buckwheat sickness is dependent on a sensitizing of the skin by means of the colour material contained in the ingested grain.

H.—THERAPY.

The local treatment of carcinomatosis and tuberculosis of the skin by means of sensitizing materials was first undertaken by Tappeiner and Jesionek (85) in 1903. They produced necrosis and separation of the affected tissues. Very encouraging communications were later received from Jesionek and from Neisser and Halberstädter (81). The latter found that the reaction on tuberculous and other tissues, even deep down, was more energetic and effective than with the usual Finsen treatment alone.

Theoretically, other effects may be expected from the use of these sensitizers. Dreyer, Neisser and Halberstädter rightly bring forward

the fact that with many sensitizing materials even red, yellow, and green rays produce active results—the very rays, that is, which have the greatest penetration and the least biological activity—at least, in animals. If we, therefore, succeed in making these deeply penetrating rays, by means of sensitizing, as active in chemical power as the blue and violet, the advantages of the chemical rays are obtained without their disadvantages.

In the treatment of skin diseases the effects produced have been minimized by the weakness of the penetration of the blue rays, especially with Bang's iron lamp, which gives out chiefly ultra-violet rays, and is, therefore, only of service in superficial affections; with the Finsen apparatus, also, the deep effect is often incomplete [Neisser].

Erythrosin, lately used by Dreyer (75), promises especial advantages, owing to its slight fluorescence and its strong absorption for green. The future must show whether these promises will be realized.

The treatment of disease in general has not yet made use of the photo-dynamic activity. There is this to note, however: that Tappeiner and Jodlbauer were able to prove the weakening of diphtheria toxine in animals by photo-dynamic processes—that is, that animals previously treated with eosin or methylene-blue tolerated what would otherwise have been a lethal dose.

It is easy to follow Busck's (16) train of thought when he proposes to treat malarial patients with sun or electric baths in addition to the quinine.

RÖNTGEN AND RADIUM RAYS.

Although the Röntgen rays are much less complex than the radium rays, their physiological effect is so similar to that of radium rays—so far as is known—that, to prevent repetition, both forms of radiant energy will be here considered together. It must be remembered, however, that the Röntgen-ray tube, apart from the peculiar X rays, emits a whole series of physical phenomena, whose action on the tissues is not yet sharply defined.

The tissues react to the rays by breaking down certain tissue substances and producing a partial arrest or delay of metabolism. The decomposition products may produce an "intoxication" if they are not removed with sufficient rapidity.

I.—PENETRATING POWER.

The great penetration power of the Röntgen rays for the soft parts of the body is well known. There are different divisions of the X rays with varying penetration (corresponding roughly to the individual colours of the spectrum). Rays of more penetrative power are produced from a Röntgen tube of high vacuum—the so-called "hard"—than from a "soft" tube.

The radium rays comprise three sets of rays—the α, β, and γ rays, the latter of which are related to, or are identical with, the Röntgen rays. The α rays are very easily absorbed, amongst other things, by the mica flake which generally closes in the radium capsule. The great penetration power of β and γ rays have mostly engrossed our attention up to now. It stands to reason that here exact statements as to the method of technique are essential if we are to avoid the introduction of an "incalculable factor" in the estimation of the results of experiments such as seems almost unavoidable with the Röntgen rays, on account of the various strength of raying, different degrees of vacuum, and the various admixture of allied phenomena, such as warmth, electric discharge, etc.

II.—INFLUENCE ON DEVELOPMENT AND CELL LIFE.

A.—BACTERIA.

It appears from the very large number of researches that the X rays are only slightly bactericidal—much weaker, for example, than the ultra-violet rays of light. Many observers deny any effect at all (86, 144).

Radium rays are more actively bactericidal, but less so than those of light (87).

B.—SINGLE CELLS.

1. Plant Cells.

The flow of the protoplasm in the cells of *Vallisneria spiralis* is, according to Lapriore (88), hastened by half an hour's exposure to the X rays. With longer exposure the protoplasm is injured.

In *Bryopsis plumosa*, according to Joseph and Prowazek (89), there are also changes in the flow and morphological arrangement of the protoplasm.

2. Protozoa.

Schaudinn (90) and Joseph and Prowazek (89) have observed that the immediate sensitiveness of single-celled organisms is much less to the Röntgen rays than might be expected from the considerable physiological effect of the rays on the tissues of man. Schaudinn did not perceive any changes in *Labyrinthula macrocystis* after fourteen hours' exposure. *Paramœcia*, also, did not react at all to eight hours' Röntgen, or to forty-eight hours' radium, raying [A. Jodlbauer (91)]. The *Amœba princeps* (Ehrenberg), at first became more lively, after five to six hours less so, and after ten hours all the specimens became spherical. Other protozoa are more sensitive, showing that there are great differences in unicellular creatures in their reaction to the Röntgen rays.

C.—MULTICELLULAR ORGANISMS.

In these organisms the processes of germination and development may be considerably affected by the "rays."

1. Plants.

According to Lapriore (88), the pollen germination in *Genista* and *Darlingtonia* ceases during raying, but not permanently. On the other hand, Maldiney and Thouvenin (92) found that the seeds of bindweed, watercress, and millet, after an hour's raying, germinated several days earlier than the unexposed control seeds. Wolfenden and Forbes Ross (93) observed similar effects.

Perthes and Nathanson (94) noted a delayed development in beans (*Vicia faba*). The average length of the germ-roots, all of which were at the beginning 5 millimetres long, amounted, after a slight application of Röntgen rays or more prolonged radium exposure, to :

Days.	*Beans not Rayed.*	*With X-Ray Exposure.*	*With Radium Exposure.*
	mm.	mm.	mm.
2	78·5	35·2	22
4	121·7	42·0	24

The greater delay is, therefore, produced by the radium rays—a fact which had already been observed by Becquerel and Dauphin (95).

2. Animals.

Röntgen and radium rays produce peculiar developmental disturbances in the eggs of ascaris, the sea hedgehog, and the silkworm, on toad embryos, and triton larvæ. These changes consist in a prolonged period of cleavage and differentiation processes, which lead to grotesque malformations, and eventually to death. The embryonic cells are not killed immediately by the most intense application of the rays, but are subsequently altered in their development (94, 96 to 98).

The regeneration of an incised area is hindered if subjected to the rays some time previously.

In chickens, Perthes has shown that raying of a wing delays the development of the associated bones and feathers.

III.—INFLUENCE ON MOTOR PROCESSES.

Joseph and Provazek (89) have shown that there is a negative tropismus to the Röntgen rays in infusoria, especially in *Paramœcia caudata* and *Volvox*, as well as in *Daphne*.

IV.—EFFECT ON GENERAL NUTRITIVE CONDITIONS AND THE TRANSFORMATION OF ENERGY.

The effect on general metabolism has not yet been investigated. Considering the effect of exposure to the Röntgen rays, the Zuntz-Geppert method holds out a promise of the best results.

In animals, loss of appetite, weakness, loss of weight, cachexia, and finally death, may occur after strong raying (99).

The temperature of the body is not changed immediately by the raying (100). In skin diseases, however, slight rises in evening temperature of ½° to 1° C. may occur during the periods of raying [Baermann and Linser]. In leuchæmic patients, who often show a rise of temperature, pyrexia frequently accompanies the treatment. This corresponds, probably, to the rises in temperature which are observed to follow the injection of nuclein-containing substances. It is, of course, usual for the temperature to rise when dermatitis or ulceration complicate the application of the rays. See also p. 1232, XIV.

V.—EFFECT ON ENZYMES AND FERMENTATION PROCESSES.

A.—SLIGHT EFFECTS.

The best-known ferments, such as chymosin, were frequently subjected to the Röntgen rays without any result (91, 102).

Radium rays acted similarly (91, 102, 103). Schmidt-Nielsen, at

any rate, attributed the slight effect which he obtained in his researches to the simultaneous development of ultra-violet rays.

The effect on invertin obtained by Henri and Mayer was very weak, and only demonstrable under certain conditions.

B.—FAVOURABLE EFFECTS.

On the other hand, certain fermentations appear to be favoured by the salts of radium (105).

With radium rays, Neuberg (106) found a much more rapid destruction of albumin in an emulsion of carcinomatous material which had been rayed than in one which had not been rayed. Jul. Wohlgemuth (107) observed the same for tuberculous lung tissue. Four times as much nitrogen was freed in three days after fifteen to thirty minutes' longer exposure to radium than in the control experiments.

On the other hand, Bergell and Braunstein observed that radium raying hindered the activity of pancreatin on peptone—that is, that less tyrosin was formed than with the usual ferment action. Yet the ferment process was markedly favoured by the addition of radium bromide itself, or of radio-active water.

Lépine and Boulud have found that in animals which have been repeatedly rayed with Röntgen rays there is a marked disappearance of the glycogen of the liver. *In vitro*, there was an increase in the glycolysis of the blood and of the amylolytic function of the pancreas under the influence of the X rays (108).

C.—INVESTIGATIONS FROM THE EXPLANATORY STANDPOINT.

Although at present we stand on the threshold of our knowledge of this subject, in the light of our limited experience there is certainly much to be said in favour of Wohlgemuth's opinion that radium certainly originates many autolytic processes. Wohlgemuth endeavoured thus to explain a statement made by Schwarz (109), which suggested a wider interpretation, and accorded with the views of those investigators who believed that they had found in it the key to many of the biological effects of X and Becquerel rays.

Schwarz recorded that colour changes and a disagreeable taste occurred in the yolks of hens' eggs after exposure to radium. These changes he attributed to the splitting off of trimethylamin during a decomposition of lecithin.

Werner, Exner and Schlachta (110), in the extension of Schwarz's views, have sought in the above-mentioned phenomena for the cause of the deleterious effect which the X and Becquerel rays produce on the young cells which are rich in lecithin (tumour cells, etc.). At the same time they have produced changes in the skin typical of direct irradiation by the injection of lecithin which has been rayed by radium or Röntgen rays, or has been ozonized.

Were it permissible to explain a complex question in the presence of

a still unknown influence by a factor which has only just come to our knowledge accidentally, it must be remembered that Schwarz's observation is by no means widely accepted. Repeating Schwarz's experiments, Thies was not able to demonstrate any effect on the yolks of eggs ; and Wohlgemuth failed to find any change in pure lecithin which had been rayed.

It is therefore evident that all theories of the effects of Röntgen and radium rays which are based on the decomposition of lecithin stand on very uncertain ground.

VI.—EFFECT ON THE BLOOD.

A.—IN THE HEALTHY INDIVIDUAL.

1. Erythrocytes and Hæmoglobin.

Heinecke observed an accumulation of pigment in the spleen in mice and, to a certain extent, in guinea-pigs and rabbits, after exposure to Röntgen rays. This siderosis corresponds to a destruction of the red blood-corpuscles. However, as the pigment formation was not excessive, only a slight destruction of red blood-corpuscles was assumed. As a matter of fact, the red corpuscle count sank correspondingly little in animals (rabbits) for the first fourteen days, the hæmoglobin apparently remaining constant. Only in the third week did a real fall appear coincidently with the dermatitis. Heineke (112) himself did not lay too much stress upon these results because of the methods employed.

In his rabbits the retrogression of the hæmoglobin-containing elements is not so insignificant. The following extracts from his tables demonstrate this :

Date.	*Exposure in Hours.*	*Erythrocytes.*	*Leucocytes.*	*Hæmoglobin.*	*Remarks.*
April 22	9	6,980,000	10,300	90	—
,, 23	14	—	—	—	—
,, 24	2	7,300,000	4,000	80	Counted before exposure.
,, 25	—	5,600,000	3,300	80	—
May 2	—	6,520,000	2,250	90	Animal languid ; eyes dull ; hair fallen.
,, 5	—	4,220,000	1,850	70	—
,, 9	—	4,770,000	1,930	40	—
,, 12	—	—	—	—	Strong dermatitis on head and nape of neck.
,, 13	—	4,340,000	3,050	50	—

Linser and Helber (113) observed a moderate anæmia in dogs, rabbits, and rats, but we regard this, as Heineke (112) did himself, as secondary to the general condition of the animals. The shape of the erythrocytes, too, showed no alteration, though after long-continued exposure granulation and polychromatophilia were occasionally met with.

Bloch (126), in healthy men, after exposure for twenty minutes on six consecutive days, found as follows: Erythrocytes, from 6,205,000 to 5,475,000; hæmoglobin, from 16·68 per cent. to 15·85 per cent.

When erythrocytes are suspended in salt solution, the Röntgen rays do not produce any change (114). When blood is rayed in ligatured veins, it is unaltered (101).

The hæmoglobin-containing elements of the bone-marrow also remain uninfluenced (115).

The inference is, therefore, that the Röntgen rays do not exert any primary influence either on the hæmoglobin or on the erythrocytes.

2. Leucocytes.

In estimating the changes in the blood resulting from X rays, the leucocytes are of interest, not merely from the standpoint of pathology, but also from that of biology.

Heineke (112) has shown that the lymphoid tissues are almost specifically sensitive to the Röntgen rays.

In guinea-pigs and mice, after a three hours' exposure to the rays, the lymphoid tissues of the spleen, the lymph glands, and the skin follicles distinctly commence to disappear. The nuclei of the lymphocytes break up into chromatin granules in less than an hour. The nuclear fragments are removed by phagocytes. In twenty-four hours all the lymphoid tissue is completely altered. Some time later—after a few days—a similar process begins in the splenic pulp (polymorphonuclear leucocytes, eosinophile cells), and in the cells of the bone-marrow, the marrow becoming rich in fat and blood [Heineke (112)].

These changes in the hæmatopoietic organs correspond to a considerable fall in the leucocyte count in the blood-stream. This is manifest in the following tables. In correspondence with the predisposition of lymphoid tissue, the lymphocytes apparently succumb most rapidly. Linser and Helber give the following table for rayed dogs (113):

Date.	*X Rays in Hours.*	*Leucocyte Count.*	*Lymphocytes (per Cnt.).*	*Polynuclears (per Cent.).*	*Mononuclears and Transitionals (per Cent.).*	*Eosinophiles (per Cent.).*	*Mast Cells (per Cent.).*	*Undetermined (per Cent.).*	*Erythrocytes.*	*Platelets.*	*Hæmoglobin.*	*Body-Weight.*
February 8	—	28,600	34	58	5	2	1	—	4,590,000	354,000	90	4,920
,, 14	40	12,000	12	83	3	1	1	—	—	—	—	4,750
,, 24	60	900	10	80	4	1	—	5	4,010,000	285,000	75	4,250
March 1 ..	10	2,400	6	78	3	—	—	12	—	—	—	4,080
,, 7 ..	—	2,100	2	71	5	—	—	22	3,810,000	3,120,000	65	3,910

Similar results are recorded by Thies (111) for radium.

However, Quadrone (115) occasionally was unable to demonstrate any effect of the rays on the blood in rabbits and guinea-pigs.

As regards healthy men, Bloch observed that, after an exposure of two hours, the leucocyte count fell from 14,300 to 7,200 per centimetre.

3. Hæmolysin ; Alexin.

Linser and Helber did not notice any effect of the rays on the hæmolytic property of blood (113).

Quadrone has shown an increase of the alexin in the serum, due to the destruction of leucocytes (115).

B.—EFFECT OF RÖNTGEN RAYS ON THE BLOOD IN DISEASE, ESPECIALLY IN LEUCHÆMIA.

Since the publication of Senn's work, leuchæmia has formed a special field for the Röntgen treatment. Considerable information on the changes in the blood has been accumulated, but for the most part all allusion to the different forms of leucocytes is omitted. A good review is given by Krause (100) and Schirmer (116), and by Franke (117).

1. Erythrocytes.

During the treatment of leuchæmic patients with Röntgen rays the erythrocytes sometimes increase to double the number (100, 114, 117, 118). The hæmoglobin and the specific gravity of the blood as a whole are increased simultaneously, all in correspondence with the improvement in the general health. Pathological forms, such as megaloblasts, decrease or entirely disappear. In occasional cases, even after an excellent initial result and complete disappearance of the leucocytes, the blood-picture of pernicious anæmia is produced (119).

2. Leucocytes.

In the overwhelming majority of cases there is a striking diminution in the number of the leucocytes. A fall from 600,000 to the normal may be often met with.

The diminution usually commences after several hundred minutes of exposure. A definite fall can occur after 1,000 to 2,000 minutes of exposure [Krause (100)]. Idiosyncrasy, of course, plays a large part—as in a case of Franke's, in which the leucocytes had already fallen to one-half their number the day after the first exposure. Many authors have described a primary increase of the leucocytes, especially of the polynuclears—not a hyperleucocytosis of myelocytes—which soon gives place to a decrease. Leucocyte fragments may even appear in the circulation [Aubertin and Beaujard (120)]. This, however, is not a usual occurrence [Krause (100)].

The fact established by Heineke from experiments on animals that lymphoid tissue is first obliterated rapidly by the Röntgen rays does not closely correspond clinically with the blood-picture of leuchæmia.

The myelocytes are the first to disappear, then follow the lymphocytes. At the same time the percentage of the neutrophile polynuclears

rises. In myelogenous leuchæmia cases have been seen in which the blood-picture returns entirely to the normal (118, 121). As a rule, however, the myelocytes, even with a more normal leucocyte count, do not return to normal—a sign that there is only a symptomatic effect on the disease.

For example, the case of myelogenous leuchæmia of Cromer's given on p. 1228 shows a typical course.

In lymphatic leuchæmia there is also a return of the actual leucocyte count to normal, yet, as a rule, the individual leucocytes are not favourably affected as in myelogenous leuchæmia. The lymphocytes always gain the upper hand (100, 121).

The mast cells often decrease slowly out of proportion to the rest, and so increase their actual percentage (117, 122).

3. Researches to Explain the Decrease in the Leucocytes.

Since Heineke's work, the fall in the leucocyte count in cases of leuchæmia treated by the X rays has been referred to the action on the germ centres. Grawitz (123) showed, in 1904, that in hypisotonic 6 per cent. salt solution the leucocytes of a leuchæmic patient showed more resistance before raying than after it. Linser and Helber (113) maintained that there is a direct injury to, and destruction of, the leucocytes in the blood-stream. The reduction of the leucocytes they consider as a secondary process dependent on the primary fall of the leucocytes in the blood-stream. Firstly, the disappearance of the leucocytes in the circulation should occur before that in the germ centres. Secondly, the appearances of destruction of the white corpuscles in a hanging drop after a two hours' exposure can be directly demonstrated. But beyond all this the blood-serum of a rayed leuchæmic patient contains leucotoxic material which destroys the white blood-corpuscles. This leucotoxic action occurs as well in a test-tube as in the bodies of animals. After injecting, for example, the blood-serum of a rayed rabbit into a second rabbit, a decrease of leucocytes results instead of the increase which ought to follow that of normal serum.

The raying of well-centrifugalized, and therefore leucocyte-free, serum produces no leucotoxine. The leucotoxic material is only formed by the decomposition of leucocytes. Leucotoxine is rendered inactive if warmed for half an hour to 50 to 60° C.

The body becomes immunized to the leucotoxine with longer exposures, and this explains the rises in the leucocyte counts which are often found in the course of longer exposures [Linser and Helber (113)]. Hoffmann observed similar leucolysis after the injection into another leuchæmic of the blood-serum of a patient who had been rayed. Curschmann and Gaupp (124) confirmed and amplified the findings of Linser and Helber. Capper and Smith observed that the mononuclears were chiefly affected, and that the degree of leucolysis corresponded to the clinical improvement manifested by the patient under X rays. The phagocytic properties were unaltered. Repeated injections of a leucolytic serum obtained from a case of lymphatic leuchæmia were followed by a remarkable fall in the mononuclear leucocytes, but a partial immunity

Date.	Conditions.	Erythrocytes.	Leucocytes.	Multinuclear Neutrophiles.		Mononuclear Neutrophiles.		Multinuclear Eosinophiles.		Mononuclear Eosinophiles.		Lymphocytes.		Mast Cells.		Transitional Forms.		Remarks.
				Per Cent.	Total No.	Per Cent.	Total No.	Per Cent.	Total No.	Per Cent.	Total No.	Per Cent.	Total No.	Per Cent.	Total No.	Per Cent.	Total No.	
—	Normal	4,500,000	6,000	72·0	4,320	—	—	2·5	150	—	—	22·0	1,320	0·5	30	3·0	180	Poikilocytes; normoblasts.
Nov. 15	Before commencement	4,500,000	290,000	82·9	240,410	9·1	26,390	2·2	6,380	0·2	580	1·4	4,060	1·2	3,480	3·0	8,700	Poikilocytes; normoblasts.
,, 27	After six exposures	4,400,000	248,000	84·0	208,320	6·4	15,872	1·7	4,216	0·1	248	2·6	6,448	2·1	5,208	3·1	7,688	Poikilocytes; normoblasts.
Dec. 3	After twelve exposures	5,000,000	140,000	86·1	120,540	5·8	8,120	2·1	2,940	0·1	140	3·1	4,340	1·4	1,960	1·4	1,960	Few poikilocytes; normoblasts rare.
,, 16	After twenty exposures	5,000,000	15,500	84·3	13,067	2·1	2,940	0·1	217	—	—	7·5	1,163	1·5	232	3·2	496	No poikilocytes; normoblasts rare.
Jan. 16	After four weeks' interval	3,900,000	6,500	84·8	5,512	—	—	1·1	71	—	—	10·1	657	0·8	52	3·2	208	Normoblasts rare.
,, 31	—	—	10,000	84·7	8,470	—	—	1·4	140	—	—	8·8	880	2·4	240	2·7	270	Normoblasts rare.

to the serum soon appeared (145). On the other hand, Franke came to negative results, and finally Kleineberger and Zöppritz (125) subjected the leucotoxine to a keenly critical investigation, which led to an absolutely contradictory result, both on theoretical and experimental grounds. Avoiding repetition, it seems to us that the details of careful work make the existence of a Röntgen leucotoxine—*i.e.*, a complex cytolysin —appear improbable.

VII.—PROTEIN METABOLISM.

A.—IN THE HEALTHY INDIVIDUAL.

1. Nitrogen Excretion.

From the destruction of the lymphoid tissue by the X rays which has been described, a simultaneous increase in the excretion of nitrogen may be expected. This is clearly shown in the somewhat fragmentary communications of Baermann and Linser (101). The following table shows an increase of the nitrogen excretion in the urine of patients suffering from skin diseases who were rayed twice a day and kept on the same food :

Date.	*I.*		*II.*		*Remarks.*
	Urine Nitrogen.	Fæces Nitrogen.	Urine Nitrogen.	Fæces Nitrogen.	
	Gm.		Gm.		
December 17	12·71	Total nitrogen,	15·28	Total nitrogen,	—
,, 18	12·85	8·96 grammes ;	15·50	3·78 grammes ;	—
,, 19	12·27	2·24 grammes	15·73	0·95 gramme	—
,, 20	12·57	daily	15·19	daily	—
Average ..	12·60	Total nitrogen excretion, 14·84 grammes	15·43	Total nitrogen excretion, 16·38 grammes	— —
December 21	**13·62**	Total nitrogen,	**16·47**	Total nitrogen,	Rays applied twice each day.
,, 22	**13·35**	5·84 grammes ;	**16·92**	4·15 grammes ;	
,, 23	**13·98**	1·46 grammes	**17·95**	1·04 grammes	
,, 24	12·33	daily	15·80	daily	
Average ..	13·32	Total nitrogen excretion, 15·29 grammes	16·78	Total nitrogen excretion, 17·82 grammes	— — —
December 25	12·80	Total nitrogen,	14·66	Total nitrogen,	—
,, 26	12·41	10·28 grammes ;	15·46	4·09 grammes ;	—
,, 27	12·32	2·57 grammes	15·75	1·02 grammes	—
,, 28	12·58	daily	15·22	daily	—
Average ..	12·53	Total nitrogen excretion, 15·1 grammes	15·27	Total nitrogen excretion, 16·29 grammes	—

The loss of nitrogen which appears for the first three or four days after the raying—as, *e.g.*, in II.—is considerable, and the question is whether it can be attributed to the destruction of the lymphoid tissues, or whether there is not some peculiar effect of the X rays in increasing the disintegration of protein.

2. Uric Acid and Purin Bases.

Bloch (126) observed in a man with eczema that the excretion of purin bodies was slightly increased, and that the P_2O_5 output was relatively greater. Bloch rayed on six consecutive days for twenty minutes at a time, and found on the average :

Nature of Experiment.	*Uric Acid.*	*Purin Nitrogen.*	P_2O_5.
	Gm.	Gm.	Gm.
Before exposure	0·5690	0·0256	3·040
During ,, ...	0·6035	0·0276	3·427
After ,, ...	0·6270	0·0261	3·120

Quadrone (115), as a rule, observed an increased P_2O_5 excretion in the urine of rayed rabbits and guinea-pigs, but this was not always present. Gualdi (146) records a decreased number of leucocytes, together with an increased uric acid output.

B.—IN DISEASED CONDITIONS.

1. Nitrogen Excretion.

The facts available are confined to leuchæmia, and are few in number, and not exhaustive.

Three determining factors are at work : Firstly, the increase of nitrogen destruction shown by Baermann and Linser (101) to occur in the healthy ; then the increase in the excretion of purin bases which depends upon the destruction of the nuclein-containing leucocytes ; and finally, acting in opposition to these, the improvement which occurs in the general condition under Röntgen treatment.

Corresponding to the fall in the leucocyte count in the first days of treatment, some records show an increased nitrogen excretion during the first days of treatment (127). Later, in the same patient nitrogen retention apparently occurred with progressive improvement of the general condition.

In Königer's patient, on the other hand, excessive increases in the excretion of P_2O_5 and nitrogen followed as an effect of fourteen days' raying, simultaneously with the recession of the splenic tumour and the leucocyte count, and corresponding with the individual differences of the times at which clinically the effects of the rays were apparent.

Exact determinations of the nitrogenous balance in leuchæmic patients who have been rayed, with accompanying analysis of the fæces, are wanted.

2. Purin Metabolism.

There are numerous records which confirm the relations between the purin bodies and the nuclein-rich leucocytes. But it is only in the majority of the factors before us that there is any correspondence—*i.e.*, leucocyte production, leucocyte destruction, uric-acid formation and excretion—since the results cannot be referred to either one or the other process.

3. Uric Acid.

A rapid rise in the uric acid is often observed in the first stages of raying (128).

The following table is taken from one of Lossen and Morawitz's cases (127):

Date.	*Erythrocytes.*	*Leucocytes.*	*Nitrogen.*	*Uric Acid.*	P_2O_5.
Period before raying:			Gm.	Gm.	Gm.
November 29–31 ..	1,400,000	453,000	19·26	1·77	1·86
December 1–3 ..	1,490,000	550,100	17·88	1·69	2·10
Period of exposure:					
January 4–6 ..	—	—	21·47	2·05	3·25
,, 7–9 ..	—	—	27·40	2·99	5·40
,, 10–12 ..	—	367,000	28·65	3·15	5·10
,, 13–15 ..	—	—	23·20	1·90	4·20
,, 16–18 ..	2,768,000	270,000	16·65	1·29	2·40
,, 19–21 ..	—	—	12·80	1·26	2·10
,, 22–24 ..	3,176,000	130,000	13·20	1·40	1·60

When the leucocytes diminish at a later stage, the uric acid appears later (100, 129).

Yet Cramer (121) and Arnsperger (130) did not observe any increase in the uric acid at the time of the fall in the leucocytes, although the figures stated suggest that there was an increase. In another case, on the other hand—*e.g.*, Case I. of Morawitz and Lossen (127), as also in a case of Stursberg's (131)—no increase of uric acid excretion could be recognised, notwithstanding the fall in the leucocytosis.

Somewhat earlier—and this may be taken for the general rule for the course of purin metabolism during the raying in leuchæmia—it is possible for the appearance of the blood to return to the normal and remain so for months, and for the splenic enlargement to have disappeared during the time that a certain maintenance of weight continues under the influence of Röntgentherapy. The uric acid is generally low in this stage, and it appears that the fall occurs in those cases which are running favourably. The uric acid falls, either subsequently to an

initial rise, or quite gradually to its lower value, and there remains for a long time.

Author.	*Leucocyte Count.*	*Maximum Number.*	*Uric Acid.*	*Original Values for Uric Acid.*	*Food.*
			Gm.		
Morawitz and Lossen (127)	6,400	315,800	0·320	1·26	200 gm. veal; diet otherwise purin-free
	—	—	0·670	—	—
	—	—	0·460	—	—
Joachim and Kurpjuweit (114)	6,400	693,000	0·244	1·22	—
	9,500	—	—	—	—

The quantity of uric acid may be considerable, even in extreme leucopenia—0·9 gramme with 2,200, and 1·23 grammes with 750 leucocytes [Morawitz and Lossen (127)]—but this is an occasional occurrence towards the close of life.

The fact that a decrease in uric acid generally attends a decrease of leucocytes does not support the theory of Linser and Helber as to the disappearance of the leucocytes in the circulation, but suggests that the lessening of the leucocyte formation is a result of an influence upon the blood-forming organs.

4. Alloxur Bodies.

In this it is still less possible to define the general rule than with uric acid, either as to a proportion to the number of leucocytes, or to the excretion of uric acid. An increased excretion of xanthin bases with low uric acid values has been described under Leuchæmia (132, 134).

5. Other Diseases.

Rosenberger (132) and Stursberg (131) record observations on the excretion of uric acid and xanthin bases in pseudo-leuchæmia. The statements are too few to permit of any decisive conclusions, although no material changes have been met with.

VIII.—THE EFFECT ON THE DIGESTIVE APPARATUS.

A.—IN THE HEALTHY.

In the researches of Baermann and Linser the nitrogen assimilation was normal.

Heineke observed diarrhœa in animals after protracted exposure to the Röntgen rays, and he attributed this to changes in the follicular apparatus of the intestine.

B.—IN DISEASED CONDITIONS.

The appetite is improved in leuchæmics under Röntgen treatment [Krause, etc.]. Burghart records the occurrence of boulimia in one case (135).

Slight diarrhœa, however, has been met with in leuchæmic patients [Schleip and Hildebrand, Franke, Krause].

In tuberculous peritonitis, Urbino (14) found that the Röntgen rays produced a disappearance of the abdominal fluid.

IX.—EFFECT ON THE KIDNEYS.

The occurrence of nephritis has been observed several times in animals [Baermann and Linser], and in leuchæmia [Schleip and Hildebrand, Franke, etc.].

X.—EFFECT ON TESTES AND OVARIES.

Animals become sterile after irradiation of the testes. No spermatozoa are found in preparations of the semen or of the testis. The cells of the seminal ducts disappear (136). Radium produces these changes more rapidly [Seldin (136)].

There is obviously a definite connection in the relation of the X and Becquerel rays towards young, developing cells, an action which finds its analogy in the marked effect on embryonic development, regeneration, and on tumour cells.

Halberstädter describes similar processes of retrogressive metamorphosis in the ovaries (136).

XI.—OTHER GLANDULAR ORGANS.

Considering the elective effect of the Röntgen and radium rays on testicular tissue, it was a natural sequence to inquire into their action on other glandular organs.

Puseg, Boggs, Mayo, C. Beck, Stegmann, P. Krause, etc., record the results of raying enlarged thyroids. Pfeiffer, however, came to completely negative results from careful investigations in Brun's clinic (137). Moszkowitsch and Stegmann were able to produce a diminution in a hypertrophied prostate (138).

Fittig (139) observed satisfactory results in Mikulicz's disease (swelling of the salivary and lacrymal glands).

Researches on metabolism might be carried out on these lines. They would be helpful in the case of diseases of the thyroid gland.[1]

[1] Rudinger describes (*D. Med. W.*, 1907, No. 2) nitrogen retention as the result of raying two cases of Basedow's disease.

XII.—EFFECTS ON THE SKIN.

A.—NORMAL SKIN.

Dryness, slight pigmentation of the skin, falling of the hair, then an inflammation and infiltration of the cutis and epidermis, and finally dermatitis bullosa, and even ulceration, may follow applications of the Röntgen rays [Kienböck (142)].

The details of the histological changes cannot be here discussed. The question as to whether there is an effect upon the vessels, or, as the majority of authors hold, and which also is more probable from analogy with other organs, a primary effect on the epithelial cells must also be passed over. Detailed accounts of the dermatological appearances are given by Freund (86), Scholtz, Halkin (138), and others.

The first signs of a reaction on the skin are met with after eight to twenty days with the Röntgen rays, and much later than after radium, with which erythema can occur after only one to two days.

The actual agent is, at any rate, the Röntgen rays themselves (140, 142), and not the electric waves and discharges given off by the Röntgen tube [Freund, Schiff (141)].

Consult also Chapter V.

B.—SKIN DISEASES.

Proliferating diseases of the skin, carcinoma, lupus, and mycosis fungoides exhibit a gradual disappearance of the diseased tissue under the Röntgen-ray treatment. This corresponds with the elective effect of the rays on germ cells. It is possible that many autolytic processes play a part in the absorption of the diseased products, and also in the improvement which has been proved to occur under the raying.

Exact determinations of the changes in metabolism are urgently needed.

XIII.—THE NERVOUS SYSTEM.

Colombo (148) states that the X rays act through the sensory nerve-endings, and reflexly affect the spinal cord and cerebrum, thus constituting the *loci minoris resitentiæ* in nervous persons.

XIV.—THE NATURE OF THE REACTION FOLLOWING EXPOSURE TO X RAYS.

Edsall and Pemberton (149) point out that a previous nephritis is intensified by the X rays, and their use should therefore be restricted in metabolic disorders and during infectious conditions. A sudden demand on the organism for the complete disintegration and excretion of large

amounts of the products of broken-down tissue is often followed by halting and incomplete metabolism. This in turn results in an intoxication due to the presence of imperfectly disintegrated tissue remnants. The nitrogen and uric acid is often diminished, and the uric acid only slowly returns to the normal.

REVIEWS AND HANDBOOKS.

Brieger u. Mayer: Licht als Heilmittel. 1904.

Frankenhäuser: Das Licht als Kraft und seine Wirkung. 1902.

Bie: Die Andwendung des Lichtes in der Medizin. 1905.

Finsen: La Photothérapie. Paris, 1899.—Photo-therapy. Finsen (translated by J. H. Sequeira). Arnold.

Hammer: Ueber den Einfl. des Lichtes auf die Hauf. 1891.

Gebhardt: Die Heilkraft des Lichtes. 1898.

Kattenbraker: Das Licht als Heilverfahren, begründet durch physiol. Tatsachen und prak. Erfahrungen. 1899.

Möller: Der Einfl. des Lichtes auf die Haut. Bibl. med. 1900.

Schönenberger: Der Einfl. des Lichtes auf den tier. Organismus. Diss. Berl., 1898.

Jensen: Die physiol. Wirkungen des Lichtes. V. n. A. 240. 1904.

Rieder: Die bisherigen Erfolge der Lichttherapie. Ibid. 254. 1904.

Schickhardt: Ueber die Einwirk. des Sonnenlichtes auf den menschl. Organismus und Mikroorganismen und die hygien. Bedeutung. Friedreich's Blätter für gerichtl. Medizin. **44.** 351. 1893.

Raum: Über der Einfluss des Lichtes a. d. Bakterien und tier. Organe. Z. Hy. **6.** 312. 1889.

Maag: Ueber den Einfl. des Lichtes auf den Menschen. K. S. **33.** 609. 1903.

Freund: Grundriss der gesamten Radiotherapie. 1903.

C. S. Woodruff: Effects of Tropical Light on White Men. Rebman.

Margaret A. Cleaves: Light Energy. Rebman.

Pancoast, H. K.: X Rays in Blood Diseases. Univ. Pennsylvania Med. Bull. 1907. Bd. 19.

LITERATURE.

1. Godneff: Ueber die Permeabilität der tier. Gewebe für die chem. wirkenden Strahlen. Diss. Kasan, 1882.

2. Onimus: Pénétration de la lumière dans les tissus vivants. C. r. S. B. Sér. 10. **2.** 678. 1895.

3. Sarason: Ueber die Finsen'sche Lupusbehandl. D. M. Z. 589. **1899.**

4. Finsen: Ueber die Anwend. von konzentr. chem. Lichtstrahlen in der Medizin. Mit. Fins. Med. Lysinst. H. **3.** 1. 1903.

5. Darbois: Traitem. du lupus vulgaire suivant les indications. Thèse de Paris. **1901.**

6. Busck: Über die Durchstrahlungsmöglichkeit des Körpers. Mit. Fins. Med. Lysinst. H. **4.** 29. 1903.

7. Drossbach: Zur modernen Lichtther. D. m. W. **27.** 827. 1901.

8. Freund: Beitr. zur Physiol. der Epidermis mit Bezug auf deren Durchlässigkeit für Licht. Ar. D. S. **58.** 3. 1901.

9. Jansen: Über die Fähigkeit der bakter. Lichtstrahlen, durch die Haut zu dringen. Mit. Fins. Med. Lysinst. H. **4.** 37. 1903.

10. Busck: Ueber die relative Penetrationsfähigkeit der versch. Spektralstrahlen gegenüber tier. Gewebe. Mit. Fins. Med. Lysinstit. H. **4.** 108. 1903. See also Lenkei (13).

11. Bang: Weitere Versuche mit Eisenelektroden. D. m. W. **28.** 35. 1902.

12. Boubnoff: Ueber das Permeabilitätsverhält. der Kleiderstoffe zum chem. wirkenden Sonnenstrahl. Ar. Hy. **10.** 335. 1890.

13. Lenkei: Die Durchdringungsfähigkeit der Sonnenstrahlen durch Kleiderst. und tier. Gewebe. Z. d. p. T. **8.** 634. 1905.

14. Downes and Blunt: On the Effect of Light upon Bacteria and other Organisms. P. R. **26.** 488. 1877.—Downes: On the Action of Sunlight on Micro-organisms, etc. Ibid. **40.** 14. 1886.

15. Duclaux: Infl. de la lumière du soleil sur la vitalité des germes des microbes. C. r. A. S. **100.** 119. 1885; **101.** 395. 1885.—Sur la durée de la vie chez les germes des mikrobes. A. c. p. **5.** 57. 1885. VI. Sér.—Arloing: Infl. du soleil sur la végétabilité des spores du Bacillus anthracis. C. r. A. S. **101.** 511. 1885. —Infl. du soleil sur la végétation, la végétabilité et la virulencê des cultures du B. anthracis. C. r. A. S. **101.** 535. 1885.—Infl. de la lumière blanche et de ses rayons constituants sur le dével. et les propriétés du B. anthracis. Ar. P. **7.** 209. 1886.—Les spores du B. anthracis sont réellement tuées par la lumière solaire. C. r. A. S. **104.** 701. 1887.—Roux: De l'action de la lumière et de l'air. An. P. **1.** 445. 1887.—Dieudonné: Beitr. zur Beurteil. der Einwirk. des Lichtes auf Bakterien. A. k. G. **9.** 405. 1894.—Kruse: Ueber die hygien. Bedeut. des Lichtes. Z. Hy. **19.** 313. 1895.—Bang: Ueber die Verteil. bakterien. Strahlen im Spektrum des Kohlenbogenlichtes. Mit. Fins. Med. Lysinst. H. **9.** 164. 1905.—Bie: Ist die bakter. Wirk. des Lichtes auf eine direkte Einwirk. auf die Bakterien oder auf eine indirekte Einwirk. durch Entwickl. eines bakter. Stoffes im Nährsubstrate zurückzuführen? Mit. Fins. Med. Lysinst. H. **9.** 75. 1905.—Bie: Ist die bakt. Fähigkeit des Lichtes ein Oxydationsprozess? Ibid. H. **9.** 5. 1905.—Richardson: Action of Light in Preventing Putrefactive Decomposition. Journ. of the Chem. Soc. Vol. **63.** 1109. 1893.

16. Boeder: Zur Frage von der Heilkraft des Lichtes. A. k. G. **17.** 165. 1900.—Jansen: Über die Fähigkeit der bakter. Lichtstrahlen, durch die Haut zu dringen. Mit. Fins. Med. Lysinst. H. **4.** 97. 1903.—Nagelschmidt: Zur Theorie der Lupusheilung durch Licht. Ar. D. S. **63.** 335. 1902.—Busck: Lichtbiologie. Mit. Fins. Med. Lysinst. H. **8.** 96. 1904.—Pfeffer: Pflanzenphysiol. **2.** 448. 1881.—Schmarda: Der Einfl. des Lichtes auf Infusionstierchen. Oesterr. Jahrb. **1845.**—Serrano Fatigati: Infl. des diverses couleurs sur le dévelop. de la respiration des infusoires. C. r. A. S. **89.** 959. 1879.—Pringsheim: Ueber Lichtwirk. und Chlorophyllfunktion in der Pflanze. Monatsber. d. Kgl. Preuss. Akad. d. Wiss. 1879. 532. 1880.

17. C. O. u. H. Jensen: Über die Widerstandsfähigkeit der Geschwulstzellen gegenüber intens. Licht. Mit. Fins. Med. Lysinst. H. **7.** 151. 1904.

18. Loeb: Der Heliotropismus der Tiere und seine Uebereinstim. mit dem Heliotropismus der Pflanzen. 1890.—Ueber künstliche Umwandl. positiv heliotrop. Tiere in negativ heliotrop. und umgekehrt. Ar. P. M. **54.** 81. 1893.—Ueber den Einfl. des Lichtes auf die Organbild. bei den Tieren. Ibid. **63.** 273. 1896. —Zur Theorie der physiol. Licht- und Schwerkraftwirkungen. Ibid. **66.** 439. 1897.

19. W. F. Edwards: De l'infl. des agents physiques sur la vie. 1824. P. 396.

20. Higginbothom: Infl. des agents physiques sur le dével. du têtard de la grenouille. Jour. de la Phys. de Brown-Séquard. **6.** 204. 1863.—On the Infl. of Physical Agents on the Development of the Tadpole, of the Triton, and the Frog. P. T. 431. 1850.—McDonnel: Exposé de quelques expér. concernant l'infl. des agents physiques sur le dével. du têtard de la grenouille commune. Jour. de la phys. de Brown-Séquard. **2.** 625. 1859.

21. Dutrochet: Recher. sur les enveloppes du fœtus. Mémoirs. Bruxelles, 1834. 412.

22. Schnetzler: De l'infl. de la lumière sur le dével. des larves des grenouilles. Ar. s. p. **51.** 247. 1874.

23. Yung: De l'infl. des différentes couleurs du spectre sur le dével. des animaux. C. r. A. S. **87.** 998. 1878.

24. Béclard: Note rélative à l'infl. de la lumière sur les animaux. C. r. A. S. **46.** 441. 1858.—Davison: On the Influences of Some Conditions on the Metamorph. of the Blow-fly. J. A. and P. **19.** 150. 1885.—Driesch: Entwicklungsmechan. Studien. Zeitschr. f. wiss. Zool. **53.** 160. 1892.—Féré: Note sur l'infl. de la lumière blanche et de la lumière colorée sur l'incubation des œufs de Poule. C. r. S. B. **45.** 744. 1893.

25. Hammond: Some Points relative to the Sanitary Influence of Light. The Sanitarian. **1.** 1873-1874.

26. Gorbatzéwitsch: De l'infl. de différents rayons colorés sur le dével. et la croissance des mammifères. Thèse de St. Pétersb. **1883.**

27. Pleasonton, cit. by Pöey: Infl. de la lumière sur la croissance de la vigne, des cochons et des taureaux. C. r. A. S. **73.** 1236. 1871.

28. Bidder u. Schmidt: Die Verdauungssäfte und der Stoffwechsel. 1852. 317.—Adducco: Adzione della luce sulla durata della vita. An. c. F. **10.** 38. 1889. Ser. 4. Ar. i. B. **12.** 208.

29. Engelmann: Ueber Reizung kontraktilen Protoplasmas durch plötzl. Beleuchtung. Ar. P. M. **19.** 1. 1879.—Ueber Sauerstoffaussch. von Pflanzenzellen im Mikrospektrum. Ibid. **27.** 485. 1882.—Ueber Licht- und Farbenperception niederster Organismen. Ibid. **29.** 387. 1882.—Bacterium photometricum. Ibid. **30.** 95. 1883.—Ueber tierisches Chlorophyll. Ibid. **32.** 80. 1883.—Die Erscheinungen der Sauerstoffaussch. chlorophyllhaltiger Zellen im Licht bei Anwendung der Bakterienmethode. Ibid. **57.** 375. 1894.

30. Strassburger: Wirkungen des Lichtes und der Wärme auf Schwärmsporen. Jena, 1878.—Verworn: Psychophysiol. Protistenstudien. Jena, 1889. Allge. Physiol. Jena, 1895.—Dreyer: Über die Einwirk. des Lichtes auf Infusorien. Mit. Fins. Med. Lysinst. H. **7.** 98. 1904.

31. Bert: Infl. de la lumière sur les êtres vivants. Rev. scient. **1878.** Nr. 42.

32. Graber: Fundamentalvers. über die Helligkeit- und Farbenempfindlichkeit augenloser und geblendeter Tiere. S. W. A. **87.** Abt. 1. 201. 1883.

33. Dubois: Sur la perceptions des radiations lumineuses par la peau, chez les Protées aveugles des grottes de la Craniole. C. r. A. S. **110.** 358. 1890.—Sur le mécanisme des fonctions photodermat. et photogéniques dans le Siphon du Pholas dactylus. Ibid. **109.** 233. 1889.

34. Finsen: La lumière comme Agent d'excitabilité. La photothérapie. **57.** 1899.

35. Quincke: Ueber den Einfl. des Lichtes auf den Tierkörper. Ar. P. M. **57.** 123. 1894.

36. Fletcher: The Survival Respiration of Muscle. J. P. **23.** 10. 1898.—Tissot: Étude des phénomènes de survie dans les muscles après la mort. Thèse de Paris. **1895.**

37. Moleschott u. Fubini: Einfl. gemischten und farbigen Lichtes auf die Kohlensäureaussch. der Gewebe. Mo. U. **12.** 325. 1881.—Moleschott: Ueber den Einfl. des Lichtes auf die Menge der vom Tierkörper ausgesch. Kuhlensäure. W. m. W. **5.** 681. 1855.—Moleschott u. Fubini: Einfl. gemischten und farbigen Lichtes auf die Aussch. der Kohlensäure bei Tieren. Mo. U. **12.** 266. 1881.—Fubini: Ueber den Einfl. des Lichtes auf die Kohlensäureaussch. bei den Batrachiern nach Wegnahme der Lungen. Mo. U. **12.** 100. 1881.—Selmi e. Piacentini: Rendiconti del R. Istit. Lombardo. Ser. 2. **3.** 53. 1870.—Fubini u. Spalitta: Einfl. des monochromen Lichtes auf die Ausatmung von Kohlensäure. Mo. U. **13.** 503. 1888.—Robert Pott: Über die Mengenverhält. der durch Respiration und Perspiration ausgesch. Kohlensäure bei versch. Tierspezies in gleichen Zeiträumen. Habilitationsschr. Jena, 1875.

38. Chasanowitz: Ueber den Einfl. des Lichtes auf die Kohlensäureaussch. im tier. Organismus. Diss. Königsb., 1872.

39. Pflüger: Ueber den Einfl. des Auges für den tier Stoffwechsel. Ar. P. M. **11.** 263. 1875.—Platen: Ueber den Einfl. des Auges auf den tier. Stoffwechsel. Ibid. **11.** 272. 1875.

40. Fubini u. Benedicenti: Ueber den Einfl. des Lichtes auf den Chemismus der Atmung. Beobachtungen an Tieren im Winterschlaf. Mo. U. **14.** 623. 1892.

41. Jacquet: Der respir. Gaswechsel. Er. Ph. **2.** Abt. 1. 457. 1903.

42. Speck: Ueber den Einfl. des Lichtes auf den Stoffwechsel. E. A. **12.** 1. 1879.

43. Loeb: Der Einfl. des Lichtes auf die Oxydationsvorgänge im tier. Organismus. Ar. P. M. **42.** 393. 1888.

44. Ewald: Influence of Light on the Gas Exchange in Animal Tissues. J. P. **13.** 847. 1892.

45. Fubini u. Ronchi: Ueber die Perspiration der Kohlensäure beim Menschen. Mo. U. **12.** 11. 1881.—Reiss: Recher. physiol. sur la perspiration insensible de la peau. A. D. S. **9.** 496. 1898.

46. Rubner u. Cramer: Ueber den Einfl. der Sonnenstrahl. auf Stoffzersetz., Wärmebild. und Wasserdampfabgabe bei Tieren. Ar. Hy. **20.** 345. 1899.

47. Wolpert: Ueber den Einfl. der Besonnung auf den Gaswechsel des Menschen. Ar. Hy. **44.** 322. 1902.

48. Wolpert: Ueber den Einfl. des Windes auf die Atmungsgrösse des Menschen. Ar. Hy. **43.** 21. 1902.

49. Salomon: Ueber die Wirk. der Heissluftbäder und elektr. Lichtbäder. Z. d. p. T. **5.** 205. 1902.

50. Krebs: Schwitzen in elektrischen Licht- und Heissluftkästen. D. m. W. **27.** 687. 1901.

51. Grawitz: Klin. experim. Blutuntersuchungen. Z. M. **21.** 459. 1892.—Knöpfelmacher: Ueber vasomotor. Beeinflus. der Zusammensetz. und physik. Beschaffenheit des menschl. Blutes. W. k. W. **6.** 810. 1893.—Winternitz: Über Blutveränderungen nach therm. Einflüssen. Blätter f. klin. Hydroth. **1894.** Nr. 4; **1897.** Nr. **11**; C. k. M. **1893.** 1017.—Löwy: Ueber Veränderungen des Blutes durch therm. Einflüsse. B. k. W. **33.** 909. 1896.—Ziegelroth: Das spez. Gewicht des Blutes nach starken Schweissen. Ar. p. A. **146.** 462. 1896.—Friedländer: Ueber Veränder. der Zusammensetz. des Blutes durch therm. Einflüsse. V. c. M. **1897.** 383.

52. Krebs u. Mayer: Blutbefund bei Schwitzprozeduren. Z. d. p. T. **6.** 371. 1903.

53. Bartels: Pathol. Untersuch. G. m. B. **3.** 1864.—Naunyn: Beit. zur Fieberlehre. Ar. P. **159.** 1870.—Schleich: Ueber das Verhalten der Harnstoffprod. bei künstl. Steigerung der Körpertemp. E. A. **4.** 82. 1875.—Topp: Ueber den Einfl. heisser Bäner auf den menschl. Organismus. Diss. Halle, 1893.—Formanek: Ueber den Einfl. heisser Bäder auf die Stickstoff- und Harnsäureaussch. beim Menschen. S. W. A. **101.** Abt. III. 278. 1892.

54. Hasselbalch: Die Wirk. des chem. Lichtbades auf Respiration und Blutdruck. Sk. Ar. P. **17.** 431; Mü. m. W. **53.** 882. 1906.

55. Reynolds Green: On the Action of Light on Diastase, and its Biolog. Significance. P. T. **188.** 167. 1897.

56. Emmerling: Die Einwirk. des Sonnenlichtes auf die Enzyme. B. C. G. **34.** 3811. 1901.—Weiss: cit. by Schmidt-Nielsen (57).

57. Schmidt-Nielsen: Die Wirk. des konzentrierten elektris. Bogenlichtes auf Chymosin, Chymosinogen und Antichymosin. Mit. Fins. Med. Lysinst. **9.** 233. 1905.

58. Schläpfer: Die Photoaktivität des Blutes. B. k. W. **42.** 1185. 1905.—Ueber die Photoaktivität des Kaninchenblutes. Ar. P. M. **108.** 537. 1905.

59. Fülles: Private communication.

60. Marti: Wie wirken die chem. Hautreize und Belichtung auf die Bild. der roten Blutkörperchen? V. c. M. 598. 1897.

61. Graffenberger: Über die Veränderungen, welche der Abschluss des Lichtes in der chem. Zusammensetz. des tier. Organismus und dessen N-Umsatz hervorruft. Ar. P. M. **53.** 238. 1893.

62. Schoenenberger: Der Einfl. des Lichtes auf den tier. Organismus. Diss. Berl., 1898.

63. Borissow: Ueber den Einfl. des Lichtes und der Dunkelheit auf die Zusammensetz. des Blutes. Jeshenedelnik. **1900.** Nr. 12. Zur Lehre von der Wirk. des Lichtes und der Dunkelheit auf den tier. Organismus. W. **1900.** Nr. 16. Z. d. p. T. **5.** 337. 1901.

64. Gyllenkreutz: Holmgreen's Blutuntersuch. während der Polarnacht. F. L. **19.** 190. 1884; cit. by Bie: loc. cit. Nr. 69, pp. 19, 40. See also Nr. 70.

65. Jensen: Die physiol. Wirk. des Lichtes. V. n. A. **1904.** 240.

66. Maklakoff: L'infl. de la lumière voltaïque sur les teguments du corps humain (l'insolation électrique). Arch. d'ophtal. **9.** 97. 1889.

67. Veiel: Ueber einen Fall von Eczema solare. Ar. D. S. **19.** 1113. 1887.

68. Hammer: Ueber den Einfl. des Lichtes auf die Haut. 1891.

69. Widmarck, cit. by Bie: Die Anwendung des Lichtes in der Medizin. 1905. P. 10.

70. Finsen: Über die Einwirk. des Lichtes auf die Haut. Mit. Fins. Med. Lysinst. H. **1.** 8. 1900.

71. Dreyer u. Jansen: Ueber den Einfl. des Lichtes auf tier. Gewebe. Mit. Fins. Med. Lysinst. H. **9.** 180. 1905.

72. Finsen: Les rayons chimiques et la variole. La photothérapie. P. 7. 1899. Die Behandl. der Pocken mit Ausschliessung der chem. Strahlen des Tageslichtes. Mit. Fins. Med. Lysinst. H. **3.** 113. 1903.

73. Tappeiner: Ueber die Wirk. fluores. Stoffe auf Infusorien nach Raab. Mü. m. W. **47.** 5. 1900; **48.** 1810. 1901.

74. Raab: Ueber die Wirk. fluores. Stoffe auf Infusorien. Z. B. **21.** 524. 1900.—Davidsohn: Ueber die Einwirk. verschiedener Akridinderivate auf Infusorien. Diss. München, 1899.—Jakobsohn: Ueber die Wirk. fluores. Stoffe auf Flimmerepithel. Z. B. **23.** 444. 1901.—Ullmann: Ueber die Einwirk. elektris. Bogenlichts auf Mikroorgan. in Gegenwart von fluores. Stoffen. Diss. München, 1901.

75. Dreyer: Sensibilisierung von Mikroorgan. und tier. Geweben. Mit. Fins. Med. Lysinst. H. **7.** 132. 1904.

76. Saccharoff u. Sachs: Ueber die hämolyt. Wirk. der photodynam. Stoffe. Mü. m. W. **52.** 297. 1905.

77. Tappeiner: Ueber die Wirk. fluores. Körper auf Fermente und Toxine. B. C. G. **36.** 3035. 1903.

78. Tappeiner u. Jodlbauer: Ueber die Wirk. fluores. Stoffe auf Diphtherietoxin und Tetanustoxin. Mü. m. W. **51.** 737. 1904.

79. Lichtwitz: Ueber die Wirk. fluores. Stoffe auf normale und hämolytische Sera. Mü. m. W. **51.** 1589. 1904.

80. Tappeiner: Ueber die Beziehung der photochem. Wirk. der Stoffe der Fluoreszenzreihe zu ihrer Fluoreszenzhelligkeit und ihrer Lichtempfindlichkeit. D. Ar. M. **86.** 479. 1906.—Tappeiner u. Jodlbauer: Ueber die Wirk. der photodynam. (fluoreszierenden) Stoffe auf Protozoen und Enzyme. D. Ar. M. **80.** 427. 1904.

81. Neisser u. Halberstädter: Über Lichtbehandl. nach Dreyer. D. m. W. **30.** 265. 1904.—Jesionek: Lichttherapie. Mü. m. W. **51.** 825. 1904; **51.** 965. 1904.

82. Ledoux-Lebard: Action de la lumière sur la toxicité de l'eosin. An. P. **16.** 387. 1902.

83. Straub: Ueber chem. Vorgänge bei der Einwirk. von Licht auf fluores. Substanzen (Eosin und Chinin) und die Bedeut. dieser Vorgänge für die Lichtwirk. Mü. m. W. **51.** 1903-04. Ueber den Chem. der Wirkung belichteter Eosinlösungen auf oxydable Substanzen. E. A. **51.** 1904.—Jodlbauer u. Tappeiner: Ueber die Beteiligung des Sauerstoffes bei der photodynam. Wirk. fluores. Stoffe. Mü. m. W. **51.** 1139. 1904. Die Beteiligung des Sauerstoffes bei der Wirk. fluores. Stoffe. D. Ar. M. **82.** 520. 1905. Ueber die Wirk. des Lichtes auf Fermente (Invertin) bei Sauerstoffanwesenheit. Mü. m. W. **53.** 653. 1906.—Edlefsen: Exper. Beitr. zum Stud. der oxydierenden Wirk. fluores. Stoffe. Mü. m. W. **51.** 1585. 1904.

84. Wedding: Verhandl. d. Berl. Ges. f. Anthrop. **57.** 1887. Ztschr. f. Ethnologie. **19.** 67. 1887.—Virchow: Ztschr. f. Ethnologie. **19.** 67. 1887.

85. Tappeiner u. Jesionek: Therap. Versuche mit fluores. Stoffen. Mü. m. W. **50.** 2042. 1903.

86. Freund: Radiotherapie. 1903.

87. Aschkinass u. Caspari: Ueber den Einfl. dissoziierender Strahlen auf organisierte Substanzen, insbes. über die bakterienschädigende Wirk. der Becquerelstrahlen. Ar. P. M. **86.** 603. 1901.—Pfeiffer u. Friedberger: Ueber die bakterientötende Wirk. der Radiumstrahlen. B. k. W. **40.** 640. 1903.

88. Lapriore: Azione dei raggi X. sul protoplasma della cellula vegetale vivente. Nuovi Rassegna Catania. **1897.**

89. Joseph u. Prowazek: Über die Einwirk. von Röntgenstrahlen auf einige Organismen, besonders deren Plasmatätigkeit. Z. a. P. **1.** 142. 1902.

90. Schaudinn: Ueber den Einfl. der Röntgenstrahlen auf Protozoen. Ar. P. M. **77.** 29. 1899.

91. Jodlbauer: Ueber die Wirk. photodynam. (fluoreszierender) Substanzen auf Paramäzien und Enzyme bei Röntgen- und Radiumbestrahlung. D. Ar. M. **80.** 488. 1904.

92. Maldiney et Thouvenin: De l'infl. des rayons X sur la germination. Rev. gén. de Botan. **10.** 81. 1898.

93. Wolfenden and Forbes Ross: The Effects Produced in Cultures of Microorganisms, etc. Ar. R. R. **5.**

94. Perthes: Über den Einfl. der Röntgenstrahlen und Radiumstrahlen auf die Zellteilung. D. m. W. **30.** 632. 1904.—Bordier: Infl. des rayons X sur l'évolution des vers à soie. I. Congrès pour l'étude de la radiol. et de l'ionisation. Ref. Fortschr. a. d. Geb. d. Röntgenstr. **9.** 362. 1906.

95. Becquerel: Sur quelques effets chim. produits par le rayon. du radium. C. r. A. S. **133.** 709. 1901.—Dixon: Radium and Plants. Nature. **69.** 5.

1903.—Dauphin: Infl. des rayons du radium sur le dévelop. et la croissance champignons infér. C. r. A. S. **134.** 154. 1904.

96. Bohn: Infl. des rayons du radium sur les animaux en voie de croissance. C. r. A. S. **136.** 1012. 1903.—Infl. des rayons du radium sur les œufs vierges it fécondés et sur les premiers stades du développement. Ibid. **136.** 1085. 1903.

97. Gilmann and Baetjer: Some Effects of the Röntgen Rays on the Development of Embryos. A. J. P. **10.** 1904.—Bardeen and Baetjer: The Inhibitive Action of the Röntgen Rays on Regeneration in Planarians. Jour. of Exper. Zool. **1.** 1904.—Schaper: Über die Wirk. des Radiums auf embryonale und regen. Entwicklungsvorgänge. D. m. W. **30.** 1314. 1904.

98. Schwarz: Zellteilung und Röntgenstrahlen. W. k. W. **16.** 714. 1903.

99. Kienböck: W. m. P. **1901.**—London: Zur Lehre von den Becquerelstrahlen und ihren physiol.-pathol. Bedeutungen. B. k. W. **40.** 523. 1903.—Boden: Ueber Radium. Mü. m. W. **51.** 459. 1904; Ueber Radium. Ibid. **51.** 857. 1904.—Heineke: Zur Kenntnis der Wirk. der Radiumstrahlen auf tier. Gewebe. Mü. m. W. **51.** 1382. 1904.

100. Krause: Zur Röntgenbehandl. der Leukämie und Pseudoleukämie. Fortschr. a. d. Geb. d. Röntgenstr. **8.** 383. 1904-05. Zur Röntgenbehandl. von Bluterkrankungen. Ibid. **8.** 209. 1904-05.

101. Bärmann u. Linser: Ueber die lokale und allge. Wirk. der Röntgenstrahlen. Mü. m. W. **51.** 996. 1904.

102. Schmidt-Nielsen: Die Wirk. der Radiumstrahlen auf das Chymosin. Mit. Fins. Lysinst. H. **9.** 233. 1905.

103. Bergell u. Braunstein: Ueber den Einfl. de Radiumsalze auf den ferment. Eiweissabbau. M. K. **1905.** Nr. 13.

104. Henri et Mayer: Action des radiations du radium sur les ferments solubles. C. r. S. B. **56.** 230. 1904.

105. Winternitz: Ueber die Einwirk. von Röntgenstrahlen auf tier. Gewebe. Ar. D. S. **78.** 223. 1906.

106. Neuberg: Ueber die Wirkungsweise des Radiums bei Karzinom. Ztschr. f. Krebsforsch. **2.** 171. 1904.

107. Wohlgemuth: Zur Kenntnis von der physiol. Wirkung des Radiums. B. k. W. **41.** 704. 1904.

108. Lépine et Boulud: Action des rayons X sur la nutrition. L. m. Dec., **1903.** Action des rayons X sur les tissaux animaux. C. r. A. S. **138.** 67. 1904.

109. Schwarz: Ueber die Wirk. der Radiumstrahlen. Ar. P. M. **100.** 532. 1903.

110. Werner: Zur chem. Imitation der biolog. Strahlenwirkung. Mü. m. W. **52.** 691. 1905. Über die Wirk. der Radiumstrahlen auf tier. Gewebe und die Rolle des Lezithins bei derselben. C. C. **31.** 1233. 1904. Zur Kennt. und Verwertung der Rolle des Lezithins bei der biolog. Wirk. der Radium- und Röntgenstrahlen. D. m. W. **31.** 61. 1905. Zur lokalen Sensibil. und Immunis. der Gewebe gegen die Wirkung der Radiumstrahlen. Ibid. **31.** 1072. 1905.—Schlachta: Zur chem. Imitation der biolog. Strahlenwirkung. Mü. m. W. **52.** 911. 1905. Zur Theorie der biolog. Strahlenwirkung. Mü. m. W. **52.** 1236. 1905.—Exner: Ueber die Art der Rückbild. von Karzinommetastasen unter der Einwirk. der Radiumstrahlen. W. k. W. **17.** 181. 1904.

111. Thies: Wirk. der Radiumstrahlen auf versch. Gewebe und Organe. G. M. C. **14.** 694. 1905.

112. Heineke: Ueber Einwirk. der Röntgenstrahlen auf Tiere. Mü. m. W. **50.** 2090. 1903. Ueber die Einwirk. der Röntgenstrahlen auf innere Organe. Mü. m. W. **51.** 785. 1904. Über die Einwirk. der Röntgenstrahlen auf innere Organe. G. M. C. **14.** 21. 1905.

113. Linser u. Helber: Über die Einwirk. der Röntgenstrahlen auf das Blut und Bemerkungen über die Einwirk. von Radium und ultraviol. Lichte. D. Ar. M. **83.** 479. 1905.

114. Joachim u. Kurpjuweit: Ueber die Behandl. der Leukämie mit Röntgenstrahlen. D. m. W. **30.** 1796. 1904.—Milchner u. Mosse: Zur Frage der Behandl. der Blutkrankh. mit Röntgenstrahlen. B. k. W. **41.** 1267. 1904.

115. Quadrone: Über die Wirkung der Röntgenstrahlen. C. i. M. **26.** 522. 1905.

116. Schirmer: Die bisherigen Ergeb. der Röntgenbehandl. bei Leukämie und Pseudoleukämie. Ctb. f. d. G. M. C. **8.** 31. 1905.

117. Franke: Ueber den Einfl. der Röntgenstrahlen auf den Verlauf der Leukämie. W. k. W. **1905.** Nr. 33.

118. Hoffmann: Ueber therap. Beeinfluss. der Leukämie durch Röntgenstrahlen. Mü. m. W. **51.** 225. 1904. Die Behandl. der Leukämie mit Röntgenstrahlen. Fortschr. a. d. Geb. d. Röntgenstr. **8.** 376. 1904-05.

119. Wassmuth: Fortschr. a. d. Geb. d. Röntgenstr. **9.** 72. 1905.

120. Aubertin et Beaujard: Les rayons X et les variations leucocytaires des leucémies. Ar. g. m. **1905.** Nr. 10.—Guerra: Ueber die Wirk. der Röntgenstrahlen. Mü. m. W. **51.** 2246. 1904.—Bozzolo: Ueber die Wirk. der Röntgenstrahlen auf die leukozytenprod. Organe. Mitteilung. a. d. Turiner Kgl. Med. Akad. **1904.** Ref. Blätter f. klin. Hydroth. **1904.** 260.

121. Cramer: Ueber die Behandl. der Leukämie mit Röntgenstrahlen. Fortschr. a. d. Geb. d. Röntgenstr. **9.** 115. 1905.

122. Mayer u. Eisenreich: Die Behandl. der Leukämie mit Röntgenstrahlen. Mü. m. W. **52.** 153. 1905.—Fränkel: Über die Behandl. der Leukämie mit Röntgenstrahlen. M. K. **1.** 136. 1905.—Müller: Über die Behandl. der Leukämie mit Röntgenstrahlen. Ibid. **1.** 188. 1905.

123. Grawitz: Günstige Beeinfluss. eines desolaten Leukämiefalles durch Röntgenstrahlen. Mü. m. W. **51.** 2162. 1904.

124. Curschmann u. Gaupp: Ueber den Nachweis Röntgenleukotoxins im Blute bei lymphat. Leukämie. Mü. m. W. **52.** 2409. 1905.

125. Klieneberger u. Zöppritz: Beitr. zur Frage der Bild. spezifi. Leukotoxine im Blutserum als Folge der Röntgenbestrahl. der Leukämie, der Pseudoleukämie und des Lymphosarkoms. Mü. m. W. **53.** 850. 1906.

126. Bloch: Beitr. zur Kenntnis des Purinstoffw. beim Menschen. D. Ar. M. **83.** 499. 1905.

127. Lossen u. Morawitz: Chem. und histolog. Untersuch. an bestrahlten Leukämikern. D. Ar. M. **83.** 288. 1905.

128. Heile: Ueber intravitale Beeinflussung autolyt. Vorgänge im Körper. Z. M. **55.** 508. 1904.

129. Königer: 22 K. i. M. **1905.** 185. Discussion.—Cramer: Ueber die Behandl. der Leukämie mit Röntgenstrahlen. Fortschr. a. d. Geb. d. Röntgenstr. **9.** 115. 1905.

130. Arnsperger: 22 K. i. M. **1905.** 171.

131. Stursberg: Zur Kenntnis der Röntgenstrahlenwirk. bei Leukämie und Pseudoleukämie. M. K. **2.** 192. 1906.

132. Rosenberger: Ueber die Harnsäure- und Xanthinbasenaussch. während der Behandl. der Leukämiker und eines Falles von Pseudoleukämie mit Röntgenstrahlen. Mü. m. W. **53.** 209. 1906.

133. Schleip u. Hildebrand: Beitr. zur Behandl. der myeloiden Leukämie mit Röntgenstrahlen. Mü. m. W. **52.** 396. 1905.

134. Bondzynski u. Gottlieb: Ueber Xanthinkörper im Harn des Leukämikers. E. A. **36.** 127. 1895.

135. Burghardt: 22 K. i. M. **1905.** 173.

136. Albers-Schönberg: Ueber eine bisher unbekannte Wirk. der Röntgenstrahlen auf den Organismus der Tiere. Mü. m. W. **50.** 1859. 1903.—Frieben: Hodenveränderungen bei Tieren nach Röntgenbestrahl. Mü. m. W. **50.** 2295. 1903.—Seldin: Ueber die Wirk. der Röntgen- und Radiumstrahl. auf inn. Organ. und den Gesamtorganismus der Tiere. Fortschr. a. d. Geb. d. Röntgenther. **7.** 322. 1903-04.—Scholtz: Ueber die Wirk. der Röntgen- und Radiumstrahlen. D. m. W. **30.** 909. 1904.—Halberstädter: Ueber die Einwirk. der Röntgenstrahlen auf Ovarien. B. k. W. **42.** 64. 1905.

137. Pfeiffer: Die Röntgenbehandl. des Kropfes auf Grund klin. Beobachtungen und histol. Untersuch. Be. C. **48.** 367. 1906. (Literature.)

138. Moszkowitsch u. Stegmann: Die Behandl. der Prostatahypertrophie mit Röntgenstrahlen. Mü. m. W. **52.** 1390. 1906.

139. Fittig: Röntgenbehandl. eines Falles von symmet. Erkrankung der Parotis. A. C.-Z. **1904.** Nr. 31.

140. Kienböck: Zur Pathol. der Hautveränderungen durch Röntgenbestrahl. W. m. P. **1901.**—Scholtz: Ueber den Einfl. der Röntgenstrahlen auf die Haut in gesundem und krankem Zustande. Ar. D. S. **59.** 87. 1902.—Halkin: Ueber den Einfluss der Becquerelstrahlen auf die Haut. Ar. D. S. **65.** 201. 1903.

141. Freund: Die Verwendung der Spannungselektrizität zur Behandl. von Kautkrankheiten. V. k. D. **1901.** 55.

142. Kienböck: Ueber die Einwirk. des Röntgenlichtes auf die Haut. W. k. W. **13.** 1153. 1900.

143. T. H. Milroy: Response of Developing Retina to Light and Radium Emanations. J. P. 1905. Vol. 33.

144. Rus: Influence of Röntgen Rays on Micro-organisms. Ar. Hy. 1906. P. 341.

145. Capps and Smith: Leucolytic Action of Blood Serum. J. E. M. 1907. **9.** 51.

146. Gualdi: Nuova Riv. Clin. Ter. Anno IX. H. **10.**

147. Urbino: Public. Soc. tip. fior. 1906.

148. Colombo: Action of Röntgen Rays on Central Nervous System. Z. d. p. T. 1906-07. Bd. X. P. 523.

149. Edsall and Pemberton: Nature of Toxic Reaction following Exposure to X Rays. A. J. M. S. 1907. P. 426.

150. Martin: Thyroid Gland Enlargements. B. M. J. 1906. Vol. ii. p. 691.

151. Widmer: Heilung eines Karzinoms durch Sonnenlicht. Mü. m. W. 1907. Nr. 13.

152. Tizzoni u. Bongiovanni: Radiumstrahlen unter den Mech. ihrer Wirkung. Ct. B. 1906. Bd. 42. Nr. 1 and 2.

153. Edsall and Pemberton: X Rays in Unresolved Pneumonia. A. J. M. S. 1907. Bd. 133.

CHAPTER XVI

NERVOUS AND MENTAL DISEASES

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A considerable amount of clinical evidence has been accumulated to show that nervous and mental diseases play an important part in many disorders of the metabolism. Experimental data are of little service in this connection, owing to the difficulties of technique. It is possible, however, at least to form a general idea of the connection between changes in the nervous tissues and the disorders of the metabolism.

No emphasis need be laid upon the fact that the central nervous system does not play so important a part as the liver or muscles in the chemical processes of the tissues. The former idea that nervous changes affected metabolism in a manner similar to that of muscular work has been definitely disproved through absolutely reliable experiments, showing that neither the heat production [Speck, Atwater (1)] nor the change of albumin and phosphorus [Oppenheim, Speck, Mainzer (2)] is altered by mental work or mental rest. It has been shown that changes of metabolism in the older investigations are to be referred to the unconscious action of the muscles. These indirect effects probably occur in pathological conditions. The diseases of the nervous system influence the metabolism in different ways, according to their association with paralysis or a state of irritation of the muscular system.

In addition to the muscles, other tissues may be concerned with the action of the central nervous system upon metabolism. The experiments of Claude Bernard and his successors concerning the " sugar puncture " and its dependence upon the condition of the liver, the polyuria and albuminuria of nervous origin, and Pawlow's valuable observations upon the influence of psychical phenomena on the secretions of the digestive glands, and the regulation of the heat production and heat loss in its relation to the vasomotor system, all suggest that in certain pathological conditions these tissues will function abnormally.

As a rule, it is not difficult to recognise the action of these forces in certain altered conditions of metabolism. It is often in many cases more difficult to decide whether the observed or alleged disorder is the cause

rather than the result, of the disease of the central nervous system. This connection between the nervous system and the metabolism has been emphasized in support of the hypothesis of the auto-intoxication origin of mental and nervous disorders. It is for the chemical pathologist to justify this view by further investigations. The foundations of this theory are at present not well grounded. The causes of cretinism, cholæmia, uræmia, and diabetic coma may certainly arise from alterations in the chemical changes of the tissues, but for other conditions which might be clinically placed with this group no definite evidence is forthcoming.

According to previously ascertained facts, the link between disorders of the metabolism and diseases of the central nervous system permits of a double explanation ; the anomalies may directly or indirectly result from, or constitute a cause of, the diseases in question. How far this one or the other view is based on actual investigations is the task to which we must now turn our attention.

A.—THE ENERGY EXCHANGE.

The extent of the consumption of energy in nervous and mental diseases is dependent upon the conditions of the muscular system, just as it is in the normal individual. It will be quite clear that during stages of excitement these patients consume more energy than in the periods of calm and stupor. It is also self-evident that muscular movements affect the gaseous exchange, particularly when it is remembered how the slightest contraction shows itself by an increased oxygen output (Zuntz-Geppert's method). It is, however, important to determine whether the " rest exchange " of such patients when kept in bed is subnormal, and if slight movements (tremors, tic, athetoses, etc.) are reflected in the total exchanges of the whole twenty-four hours.

The data obtained by observations upon patients do not suffice to clear up the first question. In some experiments Röhrig and Zuntz (3) noticed a lowering of the gaseous exchanges of about 30 to 40 per cent. after curare administration, and Erler and Pflüger obtained similar results after section of the spinal cord in rabbits. Frank and Voit (3), however, were unable to confirm the diminution produced by the curare. In man the results are almost equally contradictory. Von Voit (4) found in a man with a fracture of the eighth cervical vertebra and paralysis of both the extremities a CO_2 output of 38 per cent. less than that of a healthy man during slight movement, and 20 per cent. less than that of a healthy man during the night. Tigerstedt (5) determined the energy consumption of a starving hysterical woman weighing 48·5 kilogrammes. On the fifth day of a sleep lasting seven days he obtained a value of 24·69 calories per kilogramme. This closely approximates that of Johannson (6) for a period of sleep, and is 8 per cent. less than those of Sondén and Tigerstedt (6).

In a man with general muscular paralysis Kraus (7) found an oxygen consumption of 4·45 to 5·22 c.c., and a CO_2 output of 3·01 to 3·55 c.c. Magnus-Levy (8) noticed in the apathetic, stuporous period following a severe hæmorrhage an average value of 4·02 c.c. of the oxygen and 3·03 c.c. of CO_2 (case of paralysis). Müller's (9) patient with progressive muscular atrophy did not exhibit any diminution of energy.

For the present purpose the normal values of Kraus and Magnus-Levy, obtained as they are from "short" periods, are not directly applicable; if, then, we take those of Voit and Tigerstedt as a basis, it is permissible to infer that in cases of chronic muscular wasting the total energy exchange is diminished.

The reverse is not the case as regards the diseases in which the muscular system is in a lasting, or transitory, stage of irritability. Magnus-Levy (10) and Pfeiffer and Scholz (11) have been able to show that in patients with paralysis agitans the gaseous exchange is directly dependent upon the amount of the tremors, although the total daily exchange is probably not increased [Pfeiffer and Scholz (11)]. The food requirements of Pfeiffer's and Scholz's patients were not greater than for healthy persons of the same age. That is evident, because the limitation of muscular activities that is forced upon these patients by their general energy and tissue conditions compensates for the increased oxygen requirements called for by the tremors. The same might even be expected in other diseases. The total daily exchange of the epileptic is not increased, in spite of repeated convulsions, because the post-paroxysmal periods of quiet balance the increased energy exchange during the attacks.

On the other hand, when marked persistent muscular activity and bodily unrest occur, an increased exchange must be expected. In many mental disorders these anomalies of the muscular activity and the increased heat production may account for the enormous reduction of the body-weight. Of course, it is common clinical knowledge that refusal of food or water may also form a cause of the loss of weight. But sometimes other factors are at work. Numerous investigations agree as to the general nutritional condition of the insane. It sometimes deteriorates without reduced input or abnormal output of water or increased expenditure for physical work. These peculiarities are specially exhibited in patients suffering from progressive paralysis and epilepsy (12). Rosenfeld (13) has recently communicated similar results of his investigations upon patients the subjects of catatony. In spite of forced feeding, the rapidly diminished body-weight did not respond to the quantity of food. Death from inanition could not be prevented, even with an excess of food (up to 82 calories per kilogramme) and almost perfect muscular rest and undisturbed digestion. It is remarkable that, after the recovery from the psychosis, the body-weight quickly increased with a food-supply much smaller than that administered by force during the illness [Rosenfeld]. The output was augmented through muscular contractions. Rosenfeld's figures are compared in the following table:

Number of Experiment.	*Case.*	*Duration of the Feeding.*	*Calories Per Kg.*	*Weight.*	*Remarks.*
		Days.		Kg.	
I.	Woman, aged 37	10	28·7–42·0	+0·6	Diagnosis: Catatony; stupor, with refusal of food.
II. (*a*)	Man, aged 47	14	23·8–60·2	−1·1	Diagnosis: Catatony; insane ideas; self-accusations; hypochondria.
II. (*b*)	The same patient in a later stage	12	22·3–78·0	+1·3	—
III.	Man, aged 32	11	28·0–80·0	+7·6 (possible water retention)	Acute psychoses, with marked hallucinations; irregular movements; facial contortions; screaming fits. During observation the patient was kept in bed.
IV. (*a*)	Man, aged 50	8	36·0–54·7	+3·7	Catatony; stupor.
IV. (*b*)	—	2½ months	82·8–40·0	−9·6	No change observed at autopsy.

Apart from abnormal loss of water, it is certainly easy in these and similar cases to think of the presence of a poison which acts by increasing the requirements for oxygen, but there is no evidence which supports this idea. It is more correct to conceive of a primary disturbance of the heat regulation with an increased production. Rosenfeld's (13) observation of the onset of sweating after feeding through a tube indicates an anomaly of the heat loss which may occasion an increased production of heat, just as heat retention may do (14). I think that the factor of heat regulation in man should be more observed with regard to the extent of the heat production. The heat regulation is very important in relation to the diseases now under discussion, and its consideration might also point the way to a better understanding of the peculiar variations of the body-weight in other mental conditions. However, it is certain that the heat-regulating apparatus functions badly in paralytics, epileptics, and similar patients. How otherwise may the frequent variations of the temperature (apart from infectious causes) in paralysis be accounted for except as due to defective heat regulation? Similarly, how otherwise may we explain the observations of Kauffmann that in paralytics and hebephrenics the temperature increases up to 39·5° C. or more after slight muscular work (100 millikilogrammes!) or an intake of albumin? Probably the much-discussed "hysterical fever" also depends upon a primary disturbance of the heat regulation.

B.—PROTEIN METABOLISM.

Changes in the nervous system do not exert any direct influence on the metabolism of protein, neither in health nor in disease. Earlier and later investigations, which have shown the unaltered exchange of albumin during psychical rest and labour, during sleep or when awake, [E. Voit, Speck, Mainzer (16)] agree with the observations upon the influence of the stage of irritation in psychical diseases upon the exchange of albumin. In one case of nervous irritation Benedict (17) has determined the nitrogen exchange during irritation and rest without finding any difference in the protein exchange. The same negative result was met with in a case of insanity exhibiting periods of calm and excitement [Folin and Shaffer (18)]. Singer and Goodbody (19) record similar figures in a case of periodic paralysis. The possible alterations cannot be compressed into the formula : irritation of the central nervous system increases, and pathological " rest " diminishes the protein exchange. Wherever deviations from the normal occur, other factors must also play a part.

1. Hysteria.

Contrary to the supposition of Gilles de la Tourette and Chatelineau (20) that the nitrogen and urea excretion is diminished during the convulsion stage of hysteria, but normal during the intervals, it has been shown that no quantitative differences here exist [Mainzer (21)]. The numerous other observations on the metabolism of hysterical patients have also shown normal conditions.

2. Epilepsy.

Mairet and Lailler (22) suggest that the nitrogen excretion, sometimes the urea secretion, is increased during the attacks. In *status epilepticus* Krainski (23) was unable to find any constant relation between the nitrogen output and the attacks. He suggests that the urea synthesis is disturbed in these patients, and claims to have demonstrated an increase of ammonia and of carbonates in the blood. Fröhner and Hoppe have estimated the nitrogen excretion in epileptics under the influence of thyroid medication ; no change from the normal was observed.

3. Progressive Paralysis.

In four cases of progressive paralysis Otass (25) three times found an increased output of nitrogen. The urea excretion was normal. Recently Kauffmann has shown that in hunger, in over- and under-feeding, with small and average intakes of albumin, certain differences exist. In starving and in well-fed paralytics there was no departure from the conditions which obtain in healthy, or mentally diseased, individuals. With the excessive intake of 60 to 78 calories and 0·2 gramme nitrogen per kilogramme large amounts of nitrogen were

retained. With an intake of 42 calories and 0·11 to 0·13 gramme nitrogen per kilogramme some patients lost nitrogen, others maintained nitrogenous equilibrium, while others again retained small quantities of nitrogen. These are practically within the limits of normal variations. The only points of importance are that the assimilation coefficient for nitrogen is not high, and that with an excessive intake these patients find it difficult to attain nitrogenous equilibrium. During periods of overfeeding such patients retain large quantities of nitrogen.

4. Catatony.

Rosenfeld's (27) investigations upon four patients with catatony, who were fed through a tube, show a tendency to the retention of nitrogen in spite of insufficient supply of nourishment (after preceding hunger). With augmented intake the nitrogenous retention is increased. The patients do not differ in this respect from healthy persons or convalescents passing from starving or insufficient nourishment to full diet.

5. Paralysis Agitans.

The work of Leva and Pfeiffer and Scholz has entirely controverted the old idea that the protein metabolism was increased in this condition. There is no difference whatever between Pfeiffer and Scholz's patients and healthy persons of the same age. The effect of thyroid extract is the same as in the healthy individual. The intermediate metabolism of albumin is also unaffected (28).

6. Progressive Muscular Atrophy.

Müller's careful investigations show that the exchange of albumin is not pathologically altered ; it was easy to obtain a retention of nitrogen. The excretion of the nitrogenous constituents of the urine were normal. The creatinin excretion was not reduced, contrary to other investigations [Langer, Jakubowitsch, Weiss].

Spriggs (67) found in a youth, aged sixteen, upon a purin and creatin free diet, during rest in bed, the following figures :

Day.	*Nitrogen.*	*Creatinin.*	*Uric Acid.*
	Gm.	Gm.	Gm.
4	9·6	0·20	0·41
5	10·8	0·23	0·42
6	12·0	0·27	0·46

This gives the very low percentage of nitrogen excreted in the form of creatinin as 0·8, 0·9, 0·8 per cent. on the three days, while the uric acid is about normal—viz., 1·4, 1·3, 1·3 per cent.

7. Myasthenia.

Kauffmann has investigated the effect of muscular work in a case of myasthenic paralysis. In the first series the patient had an intake of 0·24 gramme nitrogen and 42·4 calories per kilogramme body-weight. During a period in which the symptoms were slight the patient retained 3·57 grammes nitrogen per day; in a period when the patient daily walked about 1,000 metres on level ground and went up twenty steps, typical signs of disease appeared, and the nitrogen retention amounted to 2·38 grammes nitrogen. In the later period, when the condition had practically disappeared, the nitrogen retention amounted to about 4·30 grammes per day. When the investigations were repeated, and during the first period the patient was supplied with 0·29 gramme nitrogen and 48·7 calories per kilogramme, 4·69 grammes nitrogen were retained each day. In the second period, during which general prostration and ptosis appeared after muscular work, there was retention of 2·26 grammes nitrogen. In the third, during perfectly good health, 5·52 grammes nitrogen. In a third series of observations the intake was only 0·14 grammes nitrogen and 44 calories per kilogramme. During the first period there was a loss of 0·28 gramme nitrogen, in the second period one of 0·96 gramme, and in the third a retention of 2·55 grammes daily. The relation between the total nitrogen, urea, and ammonia was as follows: In the days when the patient was well, the urea amounted to 82 to 86 per cent. of the total nitrogen, NH_3 nitrogen to 3·5 to 3·7 per cent. When signs of fatigue appeared, the urea diminished and the NH_3 increased; the corresponding figures are 66·66 per cent. to 62·4 to 74 per cent. urea, and 8·56, 13·23, and 9·1 per cent. NH_3 nitrogen. The urea synthesis was therefore affected during the days of fatigue. The high NH_3 figures refer to a production of abnormal acids. In fact, lactic acid was found in large quantities (0·132 gramme per litre) in the urine of the days of work as well as in the blood-serum (30). In this case, as well as in two others [Mohr, Boldt (31)], the liver was diseased, and it seems as if the appearance of the myasthenia coincided with the extent of the intermediary products of metabolism (lactic acid, Mohr). In such a case an auto-intoxication would be produced.

In a case of *myasthenia gravis*, without wasting of muscles, in a young woman, Spriggs (67) found a creatinin excretion of 0·7 gramme per day (2·6 to 3 per cent. of the total nitrogen) and an output of 0·4 gramme of uric acid (1 to 1·6 per cent. of the total nitrogen). In a healthy woman of the same age and weight resting in bed the creatinin excretion was 1 gramme (3·6 to 4 per cent. of the total nitrogen), and the uric acid 0·3 to 0·4 gramme (1·2 to 1·3 per cent. of the total nitrogen).

In myasthenia gravis it appears, therefore, that the creatinin output is definitely diminished, while the uric acid is practically normal.

8. Pseudo-hypertrophic Muscular Dystrophy.

Spriggs (66) investigated the metabolism of a man, aged twenty-nine, weighing 50 kilogrammes, the subject of this condition. Every precaution was taken as to intake, and the experiments were entirely free from technical errors. The creatinin output was diminished to about one-half of that of a control upon the same creatin-free diet. The total nitrogen excretion was diminished in some experiments in which there was a very small protein intake, but it bore no evident relation to the decreased creatinin elimination. The independence of the creatinin excretion of the excretion of nitrogen was well exemplified, and it is remarkable that on an ordinary diet the proportion of nitrogen excreted in the form of creatinin was less than normal (*cf.* Vol. I., pp. 126, 324).

C.—THE METABOLISM OF PHOSPHORUS.

"Without phosphorus no thought." This watchword was thought of during every investigation concerning the metabolism of phosphorus in diseases of the central nervous system. From older observations a connection between the phosphorus excretion and mental activity had been supposed, and the amount of the phosphorus excreted was deemed to represent the total activity of the nervous tissues. It is now common knowledge that no such quantitative relations exist [von Noorden, Mainzer (32)]. In some cases the nitrogen and phosphorus excretion is delayed, and the quotient $N : P_2O_5$ reduced. Other factors than cerebral activity are at work—for instance, muscular activity and altered absorption, etc.

In *paralysis agitans* Pfeiffer and Scholz observed a loss of phosphorus with an intake of 2 to 4 grammes P_2O_5. The output was 4·6 grammes. This loss was due to the age of the patient rather than to the disease itself. Healthy old men of the same age showed a similar condition. Similarly, the alteration in the quotient $N : P_2O_5$ in several diseases (hysteria, Mainzer; nervous irritation, Folin and Schaffer) is due to extracerebral causes.

Among these factors, the first to be considered is muscular work, which certainly influences the elimination of phosphoric acid (*cf.* Vol. I., pp. 360, 427).

Secondly, the conditions of absorption and secretion in the intestines play a rôle. The influence of this upon certain forms of phosphaturia, which often are regarded as nervous in origin, is sufficiently confirmed. An abnormal secretion of hydrochloric acid is also in part responsible for the changes which result in an increased output of calcium in the urine (35). It is possible that these are the causes at work in the increased output of phosphates noted by many French authors. Further investigations are necessary, and these should include determinations of the phosphorus in the food as well as its excretion via the intestine.

D.—THE CARBOHYDRATE METABOLISM.

The occurrence of spontaneous, transitory, or purely diabetic, glycosuria is rare. The glycosuria is either the consequence or the cause of the nervous disease, or both arise from the same basis (neuropathic predisposition). Traumatic neuroses with glycosuria are the most common ; next come the localized lesions ; while the spinal cord changes and the functional neuroses occupy a third place. Pure psychoses do not appear to have much connection with diabetes, except progressive paralysis, about which, however, there has been considerable discussion [Naunyn, Siegmund (37)].

In this state of affairs it is not surprising that alimentary glycosuria is specially frequent in traumatic neuroses [von Jaksch, Strümpell, Strauss, von Oordt], although the other organic or functional diseases of the central nervous system do not predispose to alimentary glycosuria to a higher degree than diseases of other organs do [von Noorden (39)]. The psychoses can in this respect be divided into two groups : the so-called degeneration psychoses exhibit a normal tolerance for carbohydrates (idiocy, mania, paranoia, epilepsy, chronic alcoholism from cerebral changes) ; others, the acquired psychoses, show diminished tolerance (amentia, senile dementia, paralysis, delirium tremens) [Raimann, Arndt (40)].

The frequent occurrence of glycosuria in nervous diseases has its analogy in experimental conditions. Claude Bernard's " puncture diabetes " is supposed to act through the liver, although the participation of the pancreas and other organs cannot be entirely excluded. Extirpation of the first, second, and third sympathetic ganglia, the cœliac ganglion, section and stimulation of the cord at the level of the brachial plexus, stimulation of the central and of the divided vagus, or the depressor nerve, or the ansa of Vieussens, section of the sciatic—all induce a glycosuria which may persist for a few hours or a few days. Glycosuria may also accompany cerebral hæmorrhages, or pontine growths, or tumours in the medullary region. Apart from the fourth ventricle, which, after all, is not a very usual situation in man, there is not any special seat of election. Cases of traumatic diabetes do occur in which no morbid changes are found to account for the glycosuria. Some cases may be associated with distinct bulbar symptoms, but in others no such indications appear.

An attempt has been made to differentiate the transitory nervous forms of glycosuria from diabetes, but so far as man is concerned this is not possible. Of course, glycosuria may exhibit some connection with certain nervous conditions, but this is by no means always the case. Many nervous diseases frequently lead to a pure diabetes, and transitional forms also occur [Naunyn].

The liver appears to be chiefly concerned in these nervous forms of diabetes. How far the pancreas may be involved is not determined. Wille investigated a number of cases of alimentary glycosuria occurring in the course of nervous diseases, and only found changes in the pancreas in two cases of cerebral hæmorrhage (41).

E.—DIGESTIVE ORGANS.

The question of auto-intoxication and the relation of the nervous system thereto is dealt with in the section on Stomach and Intestines. Here we are only concerned with the effect of nervous and mental diseases upon the alimentary functions. General everyday experience teaches that the nervous patient frequently complains of stomach and intestinal troubles when no objective signs can be found. Similarly, alterations in the secretions and the motility occur in functional and organic nerve diseases without any definite cause being present. But there are no general rules whether a certain disease is followed by increased or diminished secretion. This is also the case in the psychoses, although such might be expected from the results of Pawlow's investigations upon the dependence of the gastric secretion on nervous influences. Riva (42) found that in pellagra and stupor the hydrochloric acid was diminished. In fourteen melancholics von Noorden (42) observed increased motility, hyperacidity, sufficient digestion of protein, and no hypersecretion in the fasting condition.

Leubuscher (42) records that in twelve cases of melancholia the production of acid was now raised, now diminished. In five cases of mania hyperchlorhydria was present. In paralysis and paranoia there were no changes worthy of note. Intellectual processes are without effect, but in conditions of chronic lesions of the motor and psychical apparatus, mental decay, and paralytic attacks, the acidity is decreased. Cases of catatony and muscular irritation show a tendency to hyperchlorhydria, while the gradual mental decline in paralysis is associated with a fall in the amount of acid secreted. Functional psychoses with subsequent dementia also exhibit hypochlorhydria.

Grabe was able to obtain but small variations from the normal. In mania he observed hyperacidity, in paralysis very irregular grades of acidity. The motility was increased, but the digestion of starch was delayed by the high percentage of acid present.

Richardson found small amounts of free hydrochloric acid, much organic acid and acid salts, and a good motility in melancholia simplex. In melancholia agitata with depression or abnormal irritability, the gastric juice contained an excess of free hydrochloric acid and organic acids, and the motility was decreased.

Jaschtschenko states that in secondary forms of dementia there are no abnormal changes, but that the acidity is diminished in paralysis and the various psychoses. In melancholics with poor appetites the disturbances in the gastric digestion appear to arise from a diminution in the "appetite" secretion. Possibly the secretory nerves are at fault in this condition. Maniacs exhibit changes in the psychical as well as in the "appetite" phases of digestion. In catatony and hysteria the repression of the feelings of hunger and appetite is associated with a complete, or almost complete, failure of the "appetite" phase of the digestion. Improved secretion of gastric juice accompanies any recovery of appetite.

In paranoia, digestion, as a rule, proceeds regularly. At any rate, there is a sufficiency of " appetite " juice secreted, even when the food is given through a tube. Sometimes, however, cases do occur in which the " appetite " juice is at fault. It is possible that this is due to some " perversity " of the smell and taste.

When the food is given by a tube for long periods a special type of digestion appears, in which a juice is secreted which exhibits similar properties to those of the " appetite " juice.

F.—BLOOD.

No characteristic morphological changes occur (43). At the most, a secondary, simple, or progressive anæmia may be associated with the nervous conditions. In some cases *eosinophilia* has been observed (44), in others a *lymphocytosis* (45). These changes were, however, associated with complications of the nervous disease.

Pierce (74) recommends systematic examinations of the blood in acute mental excitement. As convalescence is approached, marked leucocytosis occurs. This fact assists diagnosis and prognosis. Gilmour (75) states that the induction of leucocytosis by the injection of nucleinic acid produces a favourable result in some cases.

The *red blood cells* are often increased—up to 8,000,000 [Kauffmann]. The *hæmoglobin* percentage rises correspondingly with the increase in the erythrocytes—up to 130 per cent. [Gowers (46)]—in hyperkinetic psychoses. The alterations in the *molecular concentration* have not yet been determined.

The *alkalinity* is decreased during epileptiform attacks. Kauffmann has estimated the alkalinity in four cases of delirium tremens and three cases of paralysis, and Loewi (50) in two cases of epilepsy. The values were considerably subnormal, ranging from 200 milligrammes NaOH to 45·2 milligrammes.

In paralytics the *fibrin content* of the blood is increased (0·2 to 1·2 per cent.); the *coagulation time* is shortened [venous blood commences to coagulate in two seconds, and is completed within thirty seconds (46)]. *Cholin* was found in a case of beri-beri by Mott and Halliburton (47). Kauffmann was unable to demonstrate this substance in the blood of a paralytic.

The presence of cholin in the blood in cases of acute degeneration of nervous tissue, and the means to be adopted for its identification, have been further investigated by Donath, Allen and French, Rosenheim, Halliburton, Reid Hunt, and others (68, 69). New tests are proposed, the one yielding the most regular results being the addition of a strong solution of iodine in potassium iodide to an alcoholic extract of 20 c.c. of blood. The characteristic crystals of periodide of cholin are formed.

Lactic acid was present in the serum withdrawn from a case of myasthenia [0·135 per cent. (48)].

Carbamic acid is stated by Krainski to be present in the blood in cases of epilepsy, and is regarded by him as responsible for the toxic characters

of the blood in this condition. He claims to have induced epileptic attacks in rabbits by the injection of blood obtained from epileptics. This and other statements as to the toxicity of the blood in epilepsy, and its content of autocytolysins and anti-autocytolysins, must be accepted with reserve (49).

Ferments.—It has been suggested that certain unusual ferments are present. These may be associated with the supposed ferment of Marinesco (70), which he attributes to the neurilemmal cells, which actively multiply during Wallerian degeneration.

Salts.—Halliburton (69) states that the *potassium* content of the blood is considerably increased in cases of acute degeneration of nervous tissues. This is what might be expected from the high percentage of potassium present in normal nervous tissues [MacCallum and Macdonald (71)].

G.—CEREBRO-SPINAL FLUID.

The cerebro-spinal fluid is the lymph of the central nervous system, and as such is a product of the metabolism of these tissues. Hence a knowledge of its composition furnishes a basis for the consideration of the pathological processes of the brain and cord (76).

Cholin is present in cerebro-spinal fluid obtained from cases of paralysis, tabes, epilepsy, and other nerve lesions (50), and is regarded as the expression of the actual degeneration of nerve substance. Gumprecht (50) demonstrated cholin in normal cerebro-spinal fluid, and the question is an open one whether there is any definite increase of cholin pathologically, or whether it is simply the total quantity of the cerebro-spinal fluid which is increased.

In a case of progressive paralysis, Donath (50) found *albumoses* and an excess of *fibrinogen*. Hofmann (51) showed that *carbamic acid*, and Füth and Lockemann (52) that *lactic acid*, was present in eclampsia.

Galactose was present in the hydrocephalus fluid removed from a child [Langstein (53)].

The *protein* and *cell content* of the cerebro-spinal fluid has been used for purposes of diagnosis. The normal secretion is poor in albumin and in cells. In inflammatory conditions of the meninges both the albumin and the cells are increased (72, 73, 76).

In acute and suppurative meningitis : excess of polymorphs.

In tuberculosis and syphilis
In tabes and general paralysis } excess of lymphocytes.

In poliomyelitis, syringomyelia, multiple neuritis, functional neurosis, and epilepsy [Stewart (72)] : no lymphocytosis.

The *pressure* of the fluid is dependent upon the amount secreted, and may be classified as follows :

Increased.

Epidemic cerebro-spinal meningitis.
Tuberculous meningitis.
Serous meningitis.
Uræmia (sometimes unchanged).

The cerebro-spinal fluid exhibits the following characteristics, which are due to the activities of the areas which it drains :

Turbid (sometimes clear), purulent meningitis.
Turbid (sometimes clear), epidemic cerebro-spinal meningitis.
Slightly turbid, or clear, tuberculous meningitis.
Clear, serous meningitis.
Clear, cerebral tumour.
Clear, abscess, uncomplicated with meningitis.

H.—URINE.

The *quantity* is increased in maniacal conditions, decreased in melancholia. It is not yet determined whether these manifestations depend only upon the water input. After epileptic and epileptiform attacks urination is frequent, and after hysterical paroxysms the urine is pale and watery.

Uric Acid.

Considerable discussion has prevailed as to the relation of uric acid to epilepsy (54). The question is not yet settled.

In chorea the uric acid is diminished (55). The vagaries of uric acid with regard to migraine, Raynaud's and all other nervous diseases, no longer gain acceptance (56).

Chlorine and Bromine.

With chlorine-rich food large amounts of bromides are rapidly excreted (59). Under these conditions the therapeutic action of bromides is delayed. When the food is poor in chlorine, bromides appear in the blood and secretions, and their elimination is lessened. In this way it is possible to some extent to substitute bromide for chlorine in the tissues.

Albumin and Albumose.

Albumin and albumose are frequently present in the urine in psychoses, acute delirium, and delirium tremens (60).

In psychoses of different types :

Köppen found albumin and albumose in				65	per cent.
Weinberg	,,	,,	,,	30	,,
Fürstner	,,	,,	,,	40	,,
Näcke	,,	,,	,,	82	,,
Liepmann (delirium tremens)				76	,,

The albuminuria or albumosuria appears late in the attack, or transitorily at the height of the excitement stage. Its intensity corresponds to the grade of irritation present.

In addition to albumoses, certain albuminous substances are

often present which are precipitated by acetic acid. This albuminuria has been considered as parallel to the "central" albuminuria of Claude Bernard.

There is considerable difference of opinion as to the relation of the appearance of albuminuria to the stage of attack in epilepsy [*cf.* Kleudgen, Fürstner, Binswanger, Voisin, Huppert]. Further observations are necessary.

Acetone.

Acetone appears in the urines of nervous or mental patients when the diet is deficient in carbohydrates, or when inanition is present (61); that is to say, the acetonuria follows the same course as it does in healthy individuals under the same conditions.

Lactic Acid.

During epileptic and eclamptic attacks, and in myasthenia, lactic acid has been observed in the urine (62, 63, 64). It is an open question whether the source of the lactic acid is the same in all these cases. In the case of eclampsia the liver was probably at fault, while in the case of epilepsy the lactic acid might have arisen from the muscles. Of course, it must be admitted that the muscles may also be indicted in eclampsia.

Toxicity.

The toxicity of the urine has been determined in several nervous diseases—paralysis by Goldflam, Crafts, Singer and Goodbody; epilepsy by Voisin, Péron, Petit, Féré, Ferranini (65). The value of the method has been seriously disputed, and at present it is impossible to accept these results without considerable reserve.

LITERATURE.

1. C. Speck: Untersuch. über die Beziehungen der geistigen Tätigkeit zum Stoffwechsel. E. A. **15.** 81-84.—Atwater, Woods, and Benedict: Metabolism of Nitrogen and Carbon in the Human Organism. U. S. D. B. **44.** (Respiration exp. No. 4. P. 51.) 1897.

2. H. Oppenheim: Beitr. zur Phys. und Path. des Harnstoffs. Ar. P. M. **23.** 446. 1880.—C. Speck: P. Nr. 1.—C. v. Voit: Phys. des Stoffw. Hermann's Handb. d. Physiologie. **6.** P. 209.—Luciani: Das Hungern. 1890.—Mainzer: Geistige Tätigkeit und Harnstoffwechsel. Monatsschr. f. Psych. u. Neurol. **1902.** —Schterbac: N- und P-Umsatz unter dem Einfluss der psychischen Tätigkeit. Ma. **1890.** P. 367.

3. Röhrig u. Zuntz: Zur Theorie der Wärmeregulation, etc. Ar. P. M. **4.** 57. 1871.—N. Zuntz: Kurarevergiftung und Stoffwechsel. Ar. P. M. **12.** 522. 1876.—O. Frank u. F. Voit: Kurare. Z. B. **41.** 309. 1901.—Erler, cit. by Voit: No. 2. P. 204.—Pflüger: Ar. P. M. **18.** 321. 1878.

4. C. v. Voit: Nr. 2. P. 204.

5. Tigerstedt: Das Minimum des Stoffwechsels beim Menschen. N. m. A. **1897.** 653.

6. Johannson: Ueber die Tagesschwankungen des Stoffwechsels. Sk. Ar. P. **8.** 85. 1898.—Sondén u. Tigerstedt: Stoffwechsel der Menschen. Sk. Ar. P. **6.** 1. 1895.

7. F. Kraus: Ueber den Einfluss von anämischen Zuständen auf den respiratorischen Gaswechsel. Z. M. **22.** 462.

8. A. Magnus-Levy: Energiehaushalt im Ruhezustand. Z. M. **60.** 214. 1906.

9. J. Müller: Progressiver Muskelatrophie. Habilit.-Schrift. Würzburg, 1896; ref. in Ar. V. **3.** 282. 1897.

10. A. Magnus-Levy: Respiratorischen Gaswechsel unter verschiedenen pathologischen Zuständen. B. k. W. **30.** 650. 1895.

11. Th. Pfeiffer u. W. Scholz: Ueber den Stoffwechsel bei der Paralysis agitans und im Senium. D. Ar. M. **63.** 368. 1899.

12. E. Mendel: Die progressive Paralyse. Berlin, 1880.—Krafft-Ebing: Progressive Paralyse. Nothnagel's Handb. d. Path. u. Ther. **9.** 37.—Binswanger: Die Epilepsie. Nothnagel's Handb. d. Path. u. Ther. **12.** I. T. 241.—Féré: Die Epilepsie. Paris, 1890.

13. Rosenfeld: Ueber den Einfl. psychis. Vorgänge auf den Stoffwechsel. Allg. Ztschr. f. Psych. u. psych.-gerichtl. Med. **63.** 367. 1906.

14. Kraus: Fever and Infection. This Handb. II., p. 90.

15. Kauffmann: Untersuch. bei der progress. Paralyse. Naturforschervers. Stuttgart. 1906.

16. Voit: Nr. 2.—Speck: Nr. 2.—Oppenheim: Nr. 2.—Mainzer: Nr. 2.

17. Benedict: N-Excretion during Nervous Excitement. A. J. P. 1902. **6.** 398.

18. Folin and Shaffer: On Phosphate Metabolism. A. J. P. **7.** 135-151.

19. Singer and Goodbody: A Case of Periodic Paralysis. Brain. **1901.** 257.

20. Gilles de la Tourette: Die Hysterie nach den Lehren der Salpetrière. **1899.** Pp. 321-330.

21. Mainzer, cit. by Binswanger: Die Hysterie. Nothnagel's Handb. Spez. Path. u. Ther. **12.** P. 673.

22. Mairet: C. r. S. B. **99.** 328. 1884.—Lailler: Ibid. **99.** 572. 1884.—Voisin: Ibid. **1892.** 332-333.—Dide et Stenuit: La polyurie et l'excrét. de l'urée dans l'épilep. N. C. **1899.** 966.—Oppenheim: Lehrb. der Nervenkrankh. 1905. Bd. II. 1214.

23. Krainski: Zur Pathol. der Epilepsie. (Russian.)—Ueber Störungen im Stoffwech. bei Epileptikern. N. C. **16.** Pp. 697, 698. 1897. Allg. Ztschr. f. Psych. u. Nervenkr. **54.** 612. 1897.

24. Fröhner u. Hoppe: Der Stoffwech. von Epileptikern unter dem Einfl. der Schilddrüsenfütterung. Psychiatr. Wochenschr. **1899.** Nr. 35.

25. Otass: Ueber Stoffwechselunters. bei Paralytikern. C. m. W. **1904.** 395.

26. Kauffmann: Nr. 15.

27. Rosenfeld: Nr. 13.

28. Leva: Klin. Beitr. zur Paralysis agitans mit Berüchsichtigung des Verhalt. des Harns. Deutsch. Ztschr. f. Nervenheilk. **2.** 75. 1891.—Pfeiffer u. Scholz: l. c. Nr. 11. (Literature.)

29. Müller: l. c. Nr. 9.—Langer: Ein Fall von progress. Muskelatrophie. D. Ar. M. **32.** 395.—Jakubowitsch: Pseudo-Hypertrophie bei Kindern. N. C. **1884.** 279.—Weiss: Ein Fall von progress. Muskelatrophie. W. m. W. 1877. 701; **1883.** 613.

30. Kauffmann: Stoffwechselunters. bei einem Fall von myasthen. Paralyse. Monat. f. Psych. u. Neurol. **20.** P. 299. 1906.

31. Mohr: Ein Beitr. zur myasthen. Paralyse. B. k. W. **1903.** Nr. 46.—Boldt: Ueber einen Fall von myasthen. Paralyse. Monat. f. Psych. u. Neurol. **20.** 39. 1906.

32. Mainzer: l. c. Nr. 2.

33. Folin and Shaffer: l. c. Nr. 18.

34. Pfeiffer and Scholz: l. c. Nr. 11.

35. Neuberg: Phosphaturia. See this Book.

36. Gilles de la Tourette: Soc. de Biol. 23 avril 1892, and l. c. Nr. 20.—Lailler: C. r. S. B. **99.** 572. 1884.—Mairet: Ibid. **99.** 328. 1884.—Schterbak: Beitr. zur Lehre von der Abhängigkeit des P-Umsatzes von gesteigerter

oder herabgesetzter Gehirntätigkeit. N. C. **10.** 171.—Féré et Herbert: C. r. S. B. 26 mars, **1892.**—Féré, Voisin, Olivière: Ibid. 23 avril, **1892.**

37. Naunyn: Der Diab. mellitus. Nothnagel's Handb. **1906.** P. 66 ff. (Full bibliography of Glycosuria and Diseases of the Nervous System.)—Siegmund: Beitr. zur Lehre der Urinveränderungen bei Geisteskrankh. Allg. Zeitschr. f. Psych., etc. **51.** 602. 1895.

38. R. v. Jaksch: Alimentäre Glykosurie. XVII. K. i. M. 1896.—v. Strümpell: Zur Aetiol. der aliment. Glykosurie. B. k. W. **1896.** Nr. 46.—Strauss: Ueber neurogene und thyreogene Glykosurie. D. m. W. **1897.** Nrs. 18, 20. Also B. k. W. **1898.** Nr. 51, and Ch. An. **22.**—Van Oordt: Aliment. Glykosurie bei Krankh. des Nervensyst. Mü. m. W. **1898.** Nrs. 1, 2. (Literature.) Mendel: Ueber das Vorkom. der aliment. Glykosurie bei Neurosen und bei den traumat. Erkrankungen des Nervensystems. Diss. Würzb., 1896.—Wille: Die aliment. Glykosurie und ihre Beziehungen zu Pankreasaffektionen. D. Ar. M. **67.** 546 ff. —Arndt: Ueber aliment. und transit. Glykosurie bei Gehirnkrankh. Z. N. **10.** 419. 1897.—Strauss: Ueber das Nebeneinandervork. von Idiotie und Diab. mell., etc. D. Ar. M. **67.** 588. 1900; Über alimentäre "spontane" und diabet. Glykosurien, etc. Z. M. 39. 1900. (Literature.)—Haedke: Ueber metatraumat. aliment. Glykosurie. D. m. W. **1900.** 501.

39. v. Noorden: Die Zuckerkrankh. und ihre Behandl. 1901. P. 22.

40. Strauss: l. c. Nr. 38.—Arndt: l. c. Nr. 38.—Raimann: Ueber Glykosurie und aliment. Glykosurie bei Geisteskranken. Z. H. **23.** 1902. 1.

41. Wille: l. c. Nr. 38.

42. Riva: N. C. **1883.** P. 141.—Grabe: St. P. **1891.** P. 30.—C. v. Noorden: Über die Magenverdauung bei Geisteskranken. Ar. P. N. **18.** 547. 1886.—Leubuscher: Über die Säureabsch. bei Nerven- und Geisteskranken. N. C. **1891.** 287.—Leubuscher u. Ziehen: Über die Salzsäureabsch. des Magens bei Geisteskranken. 1892.—Richardson: Die Sekretion bei Geisteskranken. Ma. **1902.** 673.—Jaschtschenko: Ueber die Magenverdauung mit besond. Berücksichtigung der sekretor. Funktion der Magendrüsen bei Geisteskranken. Bi. C. **1.** 224. 1903.

43. Diefendorf: Blood Changes in Dementia Paralytica. A. J. M. S. **126.** 1047 ff. 1903. (Literature.)—Sepilli: Untersuch. über das Blut von Geisteskranken. Ma. **1882.** 214.

44. Neusser, cit. by Krypiakiewicz: Über das Blut der Geisteskranken. N. C. **1892.** 489.—Bruce: On the Blood of Cases suffering from Acute Continuous Mania. J. M. Sc. 1893. XLIX. 219.

45. H. Kuhlmann: The Blood in Epilepsy. Abstr. in N. C. **1897.** 699.—Burrows: A Study of Leucocytosis associated with Convulsions. A. J. M. S. **117.** 503. 1899.—Sabrazès u. Mathis: Über den Zustand des Blutes bei Syphilis, Tabes und allge. Paralyse. C. r. S. B. **54.** 74.

46. Kauffmann: l. c. Nr. 15.

47. Mott and Halliburton: On the Blood in a Case of Beri-beri. B. M. J. July 29, **1899.**—F. W. Mott: Vier Vorlesungen aus der allge. Pathol. des Nervensystems. Deutsch von Wallach. **1902.** 67.

48. Kauffmann: l. c. Nr. 30.

49. Krainski: l. c. Nr. 23.—Mairet et Vires: Note sur la toxicité du sérum sanguin des épilept. C. r. S. B. **5.** Nr. 23. 1898.—Ceni: Ueber das Wesen und die Spezifität der im Blutserum der Epilep. enthaltenen toxischen Stoffe. Cent. f. Psych. u. Nervenh. **1905.** 213.—Ceni: Ueber einige charakter. spezifis. Antitoxine im Blutserum der Epileptiker. Ibid. 372.—Autocytotox. und Antiautocytox. im Blute der Epilept. N. C. **1903.** 398.—Ueber einige Eigentümlichkeiten der toxikolog. Wirk. des Blutes Epileptischer. Centr. f. Nervenkr. **1900.** 626.—Herter: Notes on the Toxic Properties of the Blood in Epilepsy. J. N. and M. **26.** 721. 1899.—Sala u. Rossi: Zur Frage über einige angebl. toxische und therap. Eigneschaften des Blutserums von Epileptikern. Cent. f. Nervenh. **1902.** 852.—Gerhartz: Zur Blutserumbehandl. der Epilepsie. N. C. **1904.** 835.—Wende: Erfahrung über die Blutserumbehandl. der Epilepsie. Diss. Leipzig, 1902.

50. Mott and Halliburton: l. c. Nr. 47.—F. W. Mott: l. c. Nr. 47.—Gumprecht: Cholin in der norm. und patholog. Spinalflüssigkeit und die physiol. Funktion desselben. 18 K. i. M. 324.—Donath: Das Vorkommen und die Bedeut. des Cholins in der Zerebrospinalflüssigkeit bei Epilepsie, etc. Z. p. C. **39.** 526. 1903.

51. Hofmann, cit. by Blumenthal: Ueber Zerebrospinalflüssigkeit. Er. Ph. I. Jahr. P. 285. (Literature.)

52. Füth u. Lockemann: Ueber den Nachweis von Fleischmilchsäure in der Zerebrospinalflüssigkeit Eklamp. C. G. **1906.** 41-43.—Lockemann: Ueber den Nachweis von Fleischmilchsäure in Blut, Urin und Zerebrospinalflüssigkeit eklampt. Frauen. Mü. m. W. **53.** 299.

53. Langstein: Zur Kenntnis der Zerebrospinalflüssigkeit in einem Fall von chron. Hydrocephalus. Ja. K. **58.** 925.

54. Haig: Uric Acid as a Factor in the Causation of Disease.—Krainski: l. c. Nr. 23.—Caro: Ueber die Beziehung epilept. Anfälle zur Harnsäureaussch. D. m. W. **1900.** Nr. 19.—Herter and Smith: N. Y. J. **1892.**—Hoppe: Epilepsie und Harnsäure. W. k. R. **1903.** Nr. 34.—Binswanger: l. c. Nr. 12. 237.

55. Schreiber u. Waldvogel: Beitr. zur Kenntnis der Harnsäureaussch., etc. E. A. **42.** 69. 1899.

56. Haig: l. c. Nr. 54.

57. Toulouse u. Richet: Rev. de Psych. **1900.** Nr. 1.

58. Nencki u. Siemanowsky: Das Chlor und die Halogene im Tierkörper. E. A. **34.** 313. 1894.

59. Toulouse: Ingestion du sel et élimin. de brome dans l'épilepsie. Se. m. **1904.** Nr. 46.—Laudenheimer: Verhalten der Bromsalze im Körper der Epileptiker. N. C. **16.** 538. 1897; **20.** 772. 1901.—Hondo: Zur Frage der Substitution des Chlors durch Brom. B. k. W. **1902.** Nr. 10. 205.—Hoppe: Die Beziehungen der Bromwirk. zum Stoffwech. des Epileptikers. N. C. **25.** 993. 1906.

60. Weinberg: Ueber transit. Albuminurie bei dem Delirium tremens und über Behandl. desselben. B. k. W. **1876.** Nr. 32.—Fürstner: Ueber Albuminurie bei Alkoholisten. Ar. P. N. **6.** 755. 1876.—Naecke: Beitr. zur Lehre des Delirium tremens, etc. D. Ar. M. **25.** 1880.—Köppen: Ueber Albuminurie und Propeptonurie bei Psychosen. Ar. P. N. **20.** 825. 1889.—Liepmann: Ueber Albuminurie, Albumosurie, etc. Ibid. **28.** 570. 1896.—Huppert: Albuminurie ein Symptom des epilep. Anfalls. Ar. p. A. **59.** 367.—Karrer: Zur Albuminurie bei Epilepsie. B. k. W. **1875.** 372.—Richter: Ueber das Vorkom. von Eiweiss im Urin paralytisch erkrankter Irren. Ar. P. N. **6.** 565. 1876.—Kleudgen: Albuminurie ein Symptom des epilep. Anfalls. Ar. P. N. **11.** 478.—Siegmund: l. c. Nr. 37. (Literature.)—Binswanger: l. c. Nr. 12. 235.—Voisin u. Péron: Ar. n. **23.** 353. (Literature.)

61. Hirschfeld: Über die Azetonurie und das Coma diabet. Z. M. **28.** 176. 1895; **31.** 212. 1897.—Mohr: Ueber diabet. und nicht diabet. Autointoxik. mit Säuren (Acidosis). 1904. (Literature.)—Waldvogel: Die Azetonkörper. 1904. (Literature.)—Hoppe: Ueber die Bedeut. der Azetonurie, etc. Ar. P. N. **39.** 1174. 1905. (Literature.)

62. Jnouye u. Saiki: Ueber das Auftreten abnormer Bestandteile im Harn nach epilep. Anfällen. Z. p. C. **37.** 205.—Araki: Ueber die Bild. von Milchsäure und Glykose bei Sauerstoffmangel. Ibid. **15.** 363. 1891.

63. Zweifel: Das Gift der Eklampsie und die Konsequenzen für die Behandl. Mü. m. W. **53.** 297-299.

64. Kauffmann: l. c. Nr. 30.

65. Voisin et A. Jéron: Recher. sur la toxicité des urines chez les épilept. Ar. n. **24.** 178. 1892; **25.** 65. 1893; abstr. in N. C. **1894.** 629.—Denny et Chouppe, Féré, Voisin: Soc. des hôp. **1892.** 24 juin.—Voisin: Sur la toxicité des urines chez les épileptiques avant, pendant et après les accès paroxystiques. Se. m. **1892.** 262.—Goldflam: Ueber period. familiäre Paralyse. Z. M. **19.** Suppl. 240. 1891.—Crafts: A Fifth Case of Family Periodic Paralysis. A. J. M. S. **1900.** 651.—Singer and Goodbody: l. c. Nr. 19.—Karpinsky: Ueber die Autointox. bei der Myotonie. N. C. **18.** 565. 1899.—Ferrannini: Autointossicazioni ed epilessia. Ibid. **18.** 603. 1899.—Mairet et Bosc: Recher. sur la toxicité des urines des épileptiques. Ar. P. 4. 12. **1892.**

66. Spriggs: Creatinin Output in Pseudo-hypertrophic Muscular Dystrophy. B. J. 1907. Vol. II.

67. Spriggs: Private communication.

68. Halliburton: Die Biochemie der Nerven. Er. Ph. 1905. P. 23.

69. Allen and French: Choline in Blood. J. P. and B. **10.** 1905.—Donath:

J. P. Vol. XXXIII. P. 211.—Rosenheim: J. P. Vol. XXXIII. P. 220.—Reid Hunt and Taveau: B. M. J. 1906. II. 1788.—Halliburton: Oliver-Sharpey Lectures. 1907. B. M. J. 1907. P. 1045.

70. Marinesco: P. m. Feb. 16, 1907.

71. Macallum: J. P. 1905. **32.** P. 95.—Macdonald: J. P. 1906.

72. Purves Stewart: E. M. J. 1906. P. 429.—Warrington: B. M. J. **1905.** Vol. II. P. 1017.

73. Williamson: M. Chr. 1907. P. 350.

74. Pierce: B. M. J. 1907. P. 1055.

75. Gilmour: B. M. J. 1907. P. 1056.

76. Rous: Cerebro-spinal Fluid. A. J. M. S. 1907. P. 567.

77. Mott and Halliburton: Suprarenal Glands in Nervous Diseases. Mott's Archives. Vol. III. 1907. P. 123.

78. Bodington: The Blood in General Paralysis. Mott's Archives. Vol. III. 1907. P. 143.

79. Mott: Alcohol and Insanity. Mott's Archives. Vol. III. 1907. P. 424.

80. Koch: Chemical Observations on the Nervous System in Certain Forms of Insanity. Mott's Archives. Vol. III. 1907. P. 331. (The results indicate the importance of the sulphur metabolism in nervous conditions.)

CHAPTER XVII

BONE AND JOINT DISEASES

By L. MOHR, HALLE a. S.

Translated by A. L. Edwards.

A.—GENERAL STATE OF NUTRITION—CONSUMPTION OF ENERGY.

1. Osteomalacia.

Up to the present time the minimal metabolism in osteomalacia patients has not been quantitatively determined. Information on the point is, however, desirable, as bearing upon certain theories of this disease, one of which relates to an abnormal function of the genital glands [Fehling (1)], the other to a similar affection of the thyroid gland [Hoennicks (2)].

Generally speaking, the state of nutrition is affected in proportion to the severity of the disease. As a rule, the general condition suffers from every exacerbation of the illness. The patient loses weight, and finally, from the steady progress of disease in the bones, dies of marasmus.

With amelioration of the disease, whether this be spontaneous or due to operation, or other therapeutic measures, the patient increases in weight and improves in general condition until normal health is restored. Clinical experience, however, does not justify the inference of generally abnormal metabolism. The fluctuating state of strength and nutrition is chiefly the result of insufficient nourishment, and in some cases, more particularly in cachexia, of the defective assimilation of food—as, for instance, in the second experiment by S. Neumann (3).

Where these factors can be eliminated it appears that the nourishment required by the patient is on a perfectly normal scale [von Limbeck, L. von Korczynski (4)].

2. Rickets.

The loss of weight in the early stages of the disease is, to a great extent, caused by deficient nourishment and imperfect assimilation in the intestines (diarrhœa) : hence the not infrequent appearance of fever. As soon as the first violent symptoms have subsided, and no complications (tuberculosis, enteritis, etc.) arise, the state of strength and nutri-

tion is maintained. Sometimes in well-nourished children unmistakable symptoms of rachitis are to be found.

More exact information on the requisite nourishment and metabolism in rachitic children is not forthcoming, and our knowledge of these conditions rests chiefly upon clinical observation.

B.—METABOLISM OF ALBUMIN.

1. Osteomalacia.

Von Limbeck's patient, with a daily supply of nutriment of about 9·5 grammes nitrogen, put on 7·37 grammes nitrogen in six days. Neumann's (6) patients all lost nitrogen, except in the case of the first and third, where an increase of nitrogen was observed after castration. It must be remembered, however, that in these cases, and especially in the second, the assimilation of albumin was imperfect, and that in the second case the amount of nitrogen in the food, and the number of calories, was clearly deficient. Von Korczynski's (7) first patient gained 11·99 grammes nitrogen in twenty days ; the second lost nitrogen in two different periods, during one of which ovarin was administered. In nineteen days the total loss amounted to 0·337 gramme.

The following table gives the available statistics :

Author.	*Conditions of Experiment.*	*Duration of Experiment.*	*Supply of Calories per Kg. during Experiment.*	*Daily Supply of Nitrogen.*	*Nitrogen Balance.*
		Days.			
Von Limbeck ..	—	6	Average of 980 (weight not given)	9·29–9·68	+ 7·3700
S. Neumann :					
No. 1 (*a*)	Before castration	5	—	9·620	- 13·6600
,, (*b*)	After castration	5	—	11·090	+ 2·3790
No. 2 (*a*)	Before castration	5	—	11·030	- 0·1700
,, (*b*)	Before castration	5	—	7·700	- 6·8800
,, (*c*)	After castration	5	—	4·300	- 9·5600
No. 3 (*c*)	Pregnancy before hysterectomy	5	—	10·080	- 1·1760
,, (*d*)	After parturition and hysterectomy	5	—	12·320	+ 8·8990
L. R. von Korczynski :					
No. 1 (*a*)	—	5	37 (Approximate)	19·865	+ 8·8360
,, (*b*)	—	5	32 (Approximate)	8·805	+ 0·1450
,, (*c*)	—	5	35 (Approximate)	16·479	+ 1·5300
,, (*d*)	—	5	34 (Approximate)	16·479	+ 0·4060
,, (*e*)	Ovarin tablets	4	34 (Approximate)	16·479	+ 1·0800
No. 2 (*a*)	—	5	36	17·050	+ 1·5290
,, (*b*)	—	5	37	16·340	+ 0·0704
,, (*c*)	—	5	35	16·340	- 0·3372
,, (*d*)	Ovarin six times (0·25 gm.)	4	35	16·340	- 1·5906

The proportions of the nitrogen-containing substances were not altered [Beck (8)].

Myeloma.

Segelken (9), in a case of myeloma, obtained nitrogenous equilibrium with a daily supply of 12·2 grammes nitrogen and 1,897 calories.

Arthritis Deformans.

Johannessen (9A) examined the metabolism of albumin in the case of a child with arthritis deformans, and found no serious departure from the normal. (The irregularity of the nitrogen secretions is explained by the fluctuations to which the supply of albumin was liable.) The patient retained nitrogen in large quantities.

Calcium, Magnesium, Phosphorus.

Attention has been almost invariably directed to the action of the earthy alkalis and phosphoric acids, with a view to elucidate the processes in bones and joints, and to obtain a standpoint for the consideration of osteomalacia and rickets.

(*a*) *Osteomalacia.*

Bone affected by this disease becomes impoverished in mineral elements, and gains in organic matter (10). The following figures confirm this statement (11) :

Normal bone contains .. .. .. 58·59 per cent. of fat.
Diseased bone contains .. .. .. 70·92 per cent. of fat.
(From seven-year-old osteomalacic.)

Dried at 100° C.

	Ossein.	$Ca_3(PO_4)_2$.	$CaCO_3$.	$Mg_3(PO_4)_2$.
	Per Cent.	Per Cent.	Per Cent.	Per Cent.
Normal bone contains ..	33·35	55·84	6·33	0·79
Diseased bone contains ..	50·03	38·07	6·38	0·49

The figures vary with each stage of the disease, and vary also in different bones in the same stage—*e.g.*, in the foregoing analysis the femur contained 44·97 per cent. ash and 53·03 per cent. organic matter, while the occipital bone contained 53·90 per cent. inorganic, and 46·11 per cent. organic, matter. Even when normal the different bones vary in composition, and in osteomalacia the long bones and those of the pelvis are most affected. It is an important fact that the loss of mineral matter affects all the constituent elements equally, and not the calcium especially, as stated by Mörs and Muck (12). The increase of organic matter is obtained at the expense of fat and (in the foregoing example) of osseous matter.

Author.	*Duration of Experiment.*	*Average Daily Supply.*			*Total Supply.*		
		CaO.	MgO.	P_2O_5.	CaO.	MgO.	P_2O_5.
	Days.						
Von Limbeck ..	6	0·4941	—	—	2·9649	—	—
S. Neumann :							
No. 1 (*a*)	5	2·2520	0·4035	2·7844	11·2600	2·0177	13·9920
,, (*b*)	5	2·5961	0·4277	3·2608	12·9803	2·1386	16·3040
No. 2 (*a*)	5	3·2957	0·4028	3·6162	16·4786	2·0139	18·0810
,, (*b*)	5	1·3331	0·3323	2·1902	6·6658	1·5615	10·9510
,, (*c*)	5	0·7299	0·1534	1·2515	3·6495	0·7668	6·2573
No. 3 (*a*)	5	3·9344	0·5228	3·9000	19·6720	1·6140	19·5000
,, (*b*)	5	4·1738	0·5428	4·2762	20·8690	1·7139	21·3810
,, (*c*)	5	2·4804	0·4019	2·9398	12·4022	2·0098	14·6990
,, (*d*)	5	2·8092	0·4432	3·5784	14·0459	2·2159	17·8920
L. R. von Korczynski :							
No. 1 (*a*)	5	1·2699	—	5·8828	6·3495	—	29·4140
,, (*b*)	5	1·4039	—	3·6272	7·0195	—	18·1360
,, (*c*)	5	1·0099	—	4·1496	5·0495	—	20·7840
,, (*d*)	5	1·0099	—	4·1496	5·0495	—	20·7480
,, (*e*)	4	1·0099	—	4·1496	4·0396	—	16·5984
No. 2 (*a*)	5	0·5367	—	3·7245	2·6835	—	18·6225
,, (*b*)	5	1·0062	—	4·0893	5·0310	—	20·4465
,, (*c*)	5	1·0062	—	4·0893	5·0310	—	20·4465
,, (*d*)	4	1·0062	—	4·0893	4·0248	—	16·3572
F. Sauerbruch :							
(*a*)	11	0·7880	—	2·0200	5·6000[1]	—	14·1400
(*b*)	10	0·8080	—	1·5310	5·6560[1]	—	10·7170
(*c*)	7	0·8600	—	1·8160	6·0790[1]	—	12·7130
Goldtwait, Painter, Osgood and Crudden :							
(*a*)	8	0·5700	—	1·5000	4·5600	—	12·0000
(*b*)	8	0·7200	—	—	5·7600	—	—
Hotz :							
No. 1 (*a*)	10	2·0100	—	3·5300	20·1237	—	35·3127
,, (*b*)	11	2·0500	—	3·4900	22·5594	—	38·4269
,, (*c*)	10	1·9300	—	3·4700	19·3535	—	34·7201
,, (*d*)	8	1·8900	—	3·7700	15·1857	—	30·1847
No. 2 (*a*)	8	1·3400	—	2·7600	10·7790	—	22·1478
,, (*b*)	12	1·4700	—	2·6200	17·6655	—	31·4773
,, (*c*)	7	1·3300	—	2·6200	9·3158	—	18·3888
,, (*d*)	8	1·3600	—	2·8500	10·9195	—	22·8193

[1] Calculated for seven days.

Total Expenditure.			*Balance.*			*Remarks.*
CaO.	MgO.	P_2O_5.	CaO.	MgO.	P_2O_5.	
5·6070	—	—	−2·6421	—	—	—
11·6518	2·8245	19·9289	−0·3918	−0·8068	− 6·0069	Early stage of osteomalacia.
7·1984	1·6462	9·9940	+5·7819	+0·4924	+ 6·3100	After castration.
15·8962	2·3032	13·9910	+0·5826	−0·2893	+ 4·0900	Severe form of osteomalacia before castration.
6·2018	1·8612	7·7475	+0·4640	−0·2997	+ 3·2040	After chloroform narcosis.
3·1372	0·8612	4·6962	+0·5123	+0·0944	+ 1·5611	After castration.
15·7210	2·3358	31·0420	+3·9510	−0·7218	−11·5420	Severe stage of disease.
18·1461	1·2940	11·0400	+2·7229	+0·4199	+10·3410	Improved stage of disease.
9·9687	1·7218	13·2569	+2·4335	+0·2880	+ 1·4421	Relapse in pregnancy.
12·0626	1·6208	14·5152	+1·9833	+0·5451	+ 3·3768	After hysterectomy.
4·6769	—	23·0852	+1·6726	—	+ 6·3288	Moderately severe case, which improved.
6·4806	—	16·3634	+0·5389	—	+ 1·7726	—
5·0041	—	14·7365	+0·0454	—	+ 6·0115	—
5·8235	—	16·6852	−0·7740	—	+ 4·0628	—
5·5170	—	16·0602	−1·4774	—	+ 0·5328	Six times a day, 0·25 gm. ovarin.
3·8075	—	16·9683	−1·2400	—	+ 1·6542	Severe case; incurable.
7·1800	—	19·7496	−2·1490	—	+ 0·6996	—
4·7417	—	15·6896	+0·2893	—	+ 4·7569	—
4·3917	—	13·0444	−0·3669	—	+ 3·2128	Six times a day, 0·25 gm. ovarin.
6·0700	—	11·3540	−0·4700	—	+ 2·7860	Infantile osteomalacia.
3·5490	—	8·9320	+2·1070	—	+ 1·7850	Phosphorus; cod-liver oil, 0·01; 100: 1 teaspoonful daily.
7·2420	—	11·1290	−1·1630	—	+ 1·5840	Without phosphorus.
5·6000	—	12·3200	−1·0400	—	− 0·3200	Figures quoted from Hotz.
4·0800	—	—	+1·6800	—	—	After castration.
19·5214	—	33·9380	+0·6023	—	+ 1·3747	Convalescent case.
20·2817	—	35·5047	+2·2777	—	+ 2·9222	Daily phosphorus, 1 mg.
19·8771	—	31·0229	−0·5236	—	+ 3·6972	—
15·0831	—	26·0110	+0·1026	—	+ 4·1737	—
12·7340	—	21·3248	−1·9550	—	+ 0·8230	Severe case.
17·3238	—	32·2935	+0·3417	—	− 0·8162	Daily, 1 mg. phosphorus.
9·3404	—	18·1070	−0·0246	—	+ 0·2818	—
12·1583	—	21·1377	−1·2388	—	+ 1·6816	—

The latter process is, however, not usually the case ; indeed, Schmidt (13) even asserts that in osteomalacia ossein disappears entirely from the bone. But it is possible that this statement is founded upon defective analysis, for Friedleben (14) states that to obtain glutin the bone must be subjected to exhaustive treatment with muriatic acid.

Many authorities affirm that bones in a state of osteomalacia contain lactic acid (15). Others, again, make no mention of this, and, indeed, as regards bone examined in a fresh condition, do not even admit it (16).

The chemical composition of osteomalacial bone, on which all authorities are essentially at one, excludes the possibility of lactic acid. Were a spontaneous acid present, acid salts would necessarily be found in the bone, whereas in reality there is a residuum of bases [Magnus-Levy (17)]. Moreover, the weaker and more volatile carbonic acid would be first expelled from the bone, which is not actually the case. Neither acid diminishes in greater degree than the other, but both in equal proportions.

The fate of the destroyed mineral matter may be traced in various directions: in the urinary tract, intestines, milk (18), salivary and pituitary glands, and bronchi (19). In the urinary organs calculi have frequently been found containing no urate, and consisting purely of phosphate (20).

The important function of elimination is performed by the kidneys and intestines. In the urine the excretion of P_2O_5 and Ca is now increased, now decreased (21). A knowledge of the action of these elements in osteomalacia can, however, only be obtained by simultaneous observation of their input and output. Other analyses are valueless.

The tables on pp. 1264, 1265 contain the results of the investigations made up to the present time (22). It will be seen, in the first place, that in several cases there was an actual loss of calcium at the crisis of the illness. During the stages of improvement calcium was retained. In other cases there was a deposition of calcium without any therapeutical advantage. For instance, in the second case of Neumann, described by him as very grave, and finally taking a fatal form, an increase of calcium took place ; whereas, in that reported by Senator (23), a cure was effected (by means of oophorin), in spite of increased excretion of calcium in the urine.[1] Hence it is to be inferred that this action of calcium is not peculiar to osteomalacia. Hotz states that calcium retention can be obtained by the administration of phosphorus, but that when the phosphorus is discontinued the calcium output again increases (83). I am of the opinion that, under these circumstances, it is impossible to judge of the formation or disintegration of bone merely from the changes in the calcium. Clinical investigations are far better qualified to aid in forming correct judgment both on this point and on therapeutic measures.

My view—viz., that in these cases a knowledge of the processes active in the bone cannot be obtained solely from ascertaining the metabolism of calcium—is supported by the fluctuations of phosphoric acid. It is

[1] It is possible that in this case retention of calcium occurred, but in the absence of statistics on the calcium contents of the food it cannot be definitely proved.

known that bone loses calcium and phosphoric acid in equal proportions ; hence a corresponding parallelism in their output might well be expected. This, however, does not occur, either in health or in osteomalacia. A negative calcium balance is found, together with the retention of large quantities of phosphoric acid, and a negative phosphorus balance with increase of calcium ; so that, when both elements uniformly decrease, a very grave quantitative disproportion results. Both here and in the normal organism it is extremely difficult to ascertain the true significance of the positive and negative calcium and phosphoric acid balances. Although it is probable that during emollescence of bone mineral elements are lost in urine and fæces, and during bone formation they are retained in the body, it is nevertheless indisputable that up to the present all investigations fail to afford clear proof. A true interpretation of the facts must depend on a more exact knowledge of the physiological phosphorus and calcium metabolism.

The magnesia balance is also sometimes positive, sometimes negative, without any legitimate relation being established to the clinical manifestation of the disease and to the metabolism of calcium. That a substitute of magnesium for calcium takes place in osteomalacial bone, as some assume, is out of the question (24).

(*b*) *Rickets.*

The chemical changes in the bone in rachitis are also very striking. The impoverishment of mineral elements can be so extreme that, instead of 65 per cent. inorganic matter, there is only 20 per cent. left (25). Contrary to what is the case in osteomalacia, it is chiefly the flat bones which first lose their mineral elements, and this corresponds with the observation that it is in these bones that emollescence first occurs. It may, however, be generally assumed that the whole organism suffers loss of ash constituents.

The following tables contain some comparative figures obtained by Brubacher (26) :

UNDRIED.

	Healthy Child.[1]	*Healthy Child.*[2]	*Rachitic Child*[3] (*Rachitis Congenita*).
	Per Cent.	Per Cent.	Per Cent.
Water	80·75	75·280	78·01
Fat	3·95	8·420	9·47
Ash	3·00	3·120	1·74
CaO	1·04	1·130	0·44
MgO	0·04	0·040	0·02
P_2O_5	1·09	1·150	0·67
SiO_2	0·01	0·005	0·01
Fe_2O_3	0·01	0·010	0·02

[1] Premature ; twenty-eight weeks ; height, 38 centimetres ; weight, 1,169 grammes.
[2] Stillborn ; thirty-six weeks ; height, 47 centimetres ; weight, 1,875 grammes.
[3] About eight months ; height, 41 centimetres ; weight, 1,838 grammes.

Dry Tissue, Free from Fat.

	Healthy Child.[1]	*Healthy Child.*[2]	*Rachitic Child*[3] (*Rachitis Congenita*).
	Per Cent.	Per Cent.	Per Cent.
Ash	19·60	19·11	13·94
CaO	6·83	6·95	3·53
MgO	0·30	0·22	0·28
P_2O_5	7·12	7·03	4·84
SiO_2	0·07	0·03	0·05
Fe_2O_3	0·08	0·08	0·12

In 100 Parts of the Ash.

	Healthy Child.[1]	*Healthy Child.*[2]	*Rachitic Child*[3] (*Rachitis Congenita*).
CaO	34·82	36·37	25·32
MgO	1·56	1·42	1·60
P_2O_5	36·33	36·77	34·74
SiO_2	0·37	0·17	0·39
Fe_2O_3	0·40	0·43	0·89

The figures in the case of a rachitic child were confirmed by those of three other cases analyzed by Brubacher. However, while the content of ash in the bones and in the entire organism decreases in absolute quantity, the proportion of calcium in the other parts of the body is higher in the rachitic than in the normal child (27).

Only in one child (exact age unknown, but estimated at one to two years) was it observed by Brubacher that the percentage of ash and calcium in the dry, non-adipose, muscle was rather lower than in a normal child of the same age, and that the percentage of ash in the dry, non-adipose, liver was the same as in the two other rachitic children, whereas the percentage of calcium was rather low. The few investigations that have been made of the clacium output in rachitis have led to diametrically opposite results. In the urine a normal or subnormal excretion of calcium has been observed (28). Others report an increased elimination (28). Baginsky and others found more calcium present in the fæces of rachitic than in those of normal children, with a normal figure for phosphoric acid. These observations are vitiated by the fact that they did not include the input.

The only case where a calcium balance comes into consideration is that of a twenty-month-old child with well-developed rachitis [Zweifel (29)]. His results are detailed in the following table:

[1] Premature; twenty-eight weeks; height, 38 centimetres; weight, 1,169 grammes.
[2] Stillborn; thirty-six weeks; height, 47 centimetres; weight, 1,875 grammes.
[3] About eight months; height, 41 centimetres; weight, 1,838 grammes.

	Intake of Carbonate of Lime.	*Output.*		*Total.*	*Balance.*
		Urine.	Fæces.		
Seven days' experiment: 1,900 c.c. — two-thirds milk, with 13 per cent. lactose and 1·2 per cent. salt	14·3400	0·320	3·8240	4·144	+ 10·2000
Seven days' experiment: 1,900 c.c. — two-thirds milk, with 13 per cent. lactose and 1·2 per cent. NaCl	19·4996	0·148	11·0970	11·245	+ 8·2546
Five days' experiment: 1,900 c.c. — two-thirds milk, with 13 per cent. lactose	15·0629	—	7·9955	—	+ 7·0674
Five days' experiment: 1,900 c.c. — two-thirds milk, without sugar and salt; cod-liver oil	11·0640	—	8·4918	—	+ 2·57420

Hence it is seen that the rachitic child retains even greater quantities of Ca in the body than the normal child examined by Forster (30).

(*c*) *Arthritis Deformans and Chronic Rheumatism.*

After Drachmann and Stokvis (31) had pointed out the reduction in the excretion of P_2O_5, von Noorden and Belgardt (32) found a decrease in the calcium as well as in the phosphorus output. The daily retention was as follows:

CaO	1·28 and 0·750
MgO	0·06 and 0·034
P_2O_5	1·13 and 1·130

Johannessen (33) found likewise in a child with chronic arthritis a low percentage of phosphorus in the urine (no analyses of phosphorus in fæces).

Pribram (34), in three cases of osteo-arthritis deformans, gives approximately normal figures for P_2O_5 (1·564, 2·06, and 1·648 grammes). In one case, with slight articular deformity, Pribram found 0·802 gramme P_2O_5.

Absence of information on the calcium and phosphoric acid contents of the food and fæces seriously detracts from the value of these figures. The same applies to those of M. Schüller, who found in osteo-arthritis a reduced output of calcium in the urine, together with an increase of the same in the head of the bone.

C.—ABSORPTION OF NUTRIMENT.

1. Osteomalacia.

Apparently, as long as there is no serious general disturbance the resorption of nutriment is carried on successfully. The greater the progress of the marasmus, the greater the apparent danger for food resorption. The following table includes some figures for absorption of albumin. The resorption of fat has only once been investigated [von Limbeck (35)]; it was then found normal.

Absorption.

	Nitrogen (per Cent.).		*Nitrogen (per Cent.).*
Von Limbeck (35)	93·10	Korczynski (35), No. 2 (*c*) ..	91·38
		,, ,, (*d*) ..	90·85
Korczynski (35), No. 1 (*a*) ..	92·66		
,, ,, (*b*) ..	89·40	S. Neumann (35), No. 1 (*a*) ..	86·05
,, ,, (*c*) ..	94·49	,, ,, (*b*) ..	94·94
,, ,, (*d*) ..	92·73	,, No. 2 (*a*) ..	70·75
,, ,, (*e*) ..	94·21	,, ,, (*b*) ..	70·54
,, No. 2 (*a*) ..	93·21	,, ,, (*c*) ..	64·77
,, ,, (*b*) ..	91·85	,, No. 3 (*c*) ..	89·09
		,, ,, (*d*) ..	98·19

The proportions of phosphoric acid and calcium in the fæces vary considerably. It is, nevertheless, remarkable how frequently supernormal values are met with.

Moreover, it is by no means invariably that the fæcal phosphorus runs parallel with that of calcium or with the augmentation of calcium, as is the case under normal conditions. The proportion of calcuim excretion in the fæces is, contrary to normal conditions, generally greater; but here, too, no standard can be fixed. The table given on p. 1271 will show the figures available (36).

2. Rickets.

No investigations are recorded on the assimilation of nitrogen and fat.

The assumed increased calcium output in the fæces has been stated above [Petersen, Baginski, etc.]. Zweifel (37) has recently determined the amount of calcium salts present in the fæces of a rickety child (those soluble in water as well as those soluble in ether and alcohol), both with and without fat in the diet. He found that with a greater quantity of fat in the fæces the calcium soap increased and the calcium salts soluble in water decreased, and *vice versa*. The total loss of calcium was not great.

Excretion of Phosphorus and Calcium in the Fæces.

Author.	P_2O_5 (*Percentage Intake*).	*CaO* (*Percentage Total Output*).
Von Limbeck	—	70·16
Goldtwait, Painter, Osgood and Crudden (*a*)	29·30	31·81
Ditto (*b*)	—	25·00
S. Neumann, No. 1 (*a*)	55·53	83·47
,, ,, (*b*)	23·26	89·23
,, No. 2 (*a*)	57·80	97·42
,, ,, (*b*)	49·40	85·72
,, ,, (*c*)	35·96	94·39
,, No. 3 (*a*)	63·64	96·12
,, ,, (*b*)	9·12	96·86
,, ,, (*c*)	42·65	93·03
,, ,, (*d*)	38·51	92·20
L. R. von Korczynski, No. 1 (*a*) ..	13·57	69·16
,, ,, ,, (*b*) ..	37·08	80·43
,, ,, ,, (*c*) ..	16·09	75·80
,, ,, ,, (*d*) ..	27·89	83·65
,, ,, ,, (*e*) ..	37·35	90·77
,, ,, No. 2 (*a*) ..	39·18	75·10
,, ,, ,, (*b*) ..	53·82	89·36
,, ,, ,, (*c*) ..	29·09	88·42
,, ,, ,, (*d*) ..	34·31	86·23
F. Sauerbruch (*a*)	45·90	81·98
,, (*b*)	30·76	67·82
,, (*c*)	51·90	71·40
Hotz, No. 1 (*a*)	51·15	93·14
,, ,, (*b*)	48·90	92·98
,, ,, (*c*)	52·62	92·30
,, ,, (*d*)	47·21	92·84
,, No. 2 (*a*)	57·09	90·73
,, ,, (*b*)	53·10	90·13
,, ,, (*c*)	53·60	90·95
,, ,, (*d*)	59·80	90·12

D.—BLOOD.

In osteomalacia the blood sometimes presents the characters met with in chlorosis [von Jaksch, Winckel, Eisenhardt (38)]. It is uncertain whether this has any connection with the ovaries, the removal of which, according to Breuer and Seiler, resulted in similar changes.

Apart from an increase of eosinophile cells, every variety of secondary anæmia is to be expected [Neusser]. Changes of a morphological nature bearing a resemblance to chlorotic changes have been found also in rickets [Schiff, Morse (39)]. Generally speaking, the most diverse variations occur without being peculiar to the disease (40).

Special attention has been devoted to the chemical composition of the blood.

In osteomalacia, as well as in rachitis, the presence of an acid (lactic acid) has been assumed and a loss of alkalinity presupposed, both being actually found in several cases of osteomalacia (41). Kohler, in an analysis of the ash, observed an increase of sulphuric acid and a decrease of sodium. In other cases the reaction was normal (43). The reduction of alkalinity is, as in other diseases akin to marasmus which lead to anæmia, dependent on the reduction of the protein content of the blood, and not on the presence of any particular acid.

In rickets Stöltzner (44) has demonstrated by exhaustive experiments that the alkalinity remains normal.

E.—URINE.

1. Colour.

In ochronosis urine is discharged which either is already blackish in colour, or immediately becomes so on exposure to the air. Albrecht and Zdarek found that the urine reduced Fehling's solution and ammoniacal silver solution, and observed that when chloride of iron was added to an ether extract, a transitory green colour appeared. The dark colouring of the cartilage and urine was associated with the presence of a nitrogenous substance; accordingly in this case alkapton or one of its derivatives must have been present. Langstein, on investigating the urine in a case of Hansemann's, and analyzing cartilage in a case of L. Pick's (47), found no support for the theory that the black colouring of urine and cartilage was due to alkapton; he regarded the colouring matter as melanin.

2. Lactic Acid.

In cases of osteomalacia, lactic acid has sometimes been observed in the urine, but its absence is the more general finding (48). Lactic acid occurs in other conditions, so that its presence in osteomalacia cannot be peculiar to that disease, and the authorities who report its occurrence do not thereby prove what they pathologically claim to do.

3. Bence-Jones Albumin.

In the year 1848 Bence-Jones examined the urine of a man supposed to be suffering from osteomalacia, and for the first time obtained the remarkable result that at 56° C. the urine exhibited turbidity which disappeared on boiling, reappearing on cooling. He was further enabled to show that the urine, with nitric acid and other mineral acids, even when cold yielded a precipitate, which disappeared on the application of heat and reappeared on cooling. As Dalrymple (50) reports, it is here no question of osteomalacia, but rather of myelomatosis. Since that time more than one hundred similar investigations have been made (51).

Bence-Jones, Kühne, Huppert, etc. (52), were of opinion that the matter found in the urine was an albumose; Magnus-Levy has shown that it is a pure albumin. Its albuminous nature has recently been confirmed by Abderhalden and Rostoski (54), in that they have succeeded, by submitting the substance to hydrolysis, in extracting tyrosin. Moreover, Grutterink and de Graaff (55) have succeeded in crystallizing this substance. It is often excreted in the urine in large quantities—15 to 36 grammes [Magnus-Levy, etc.]—but the amount varies in different cases. In Magnus-Levy's (56) case, the quantity amounted to 40 per cent. of the total nitrogen. Occasionally ordinary albumin occurred in the urine. The substance has been also found in the medulla of the diseased bone [Parkes Weber, Hutchison and Macleod (57)]; in the blood, exudation, and lymphatic glands [H. Ellinger (58)].

After careful calculation Magnus-Levy felt satisfied that the substance could not possibly originate in the diseased medulla, and therefore attributed its origin to metamorphosis of the albumin contained in the food, but up to the present it has only once been proved that the quantitative secretion of Bence-Jones albumin depends directly on the presence of albumin in the food [Voit and Salvendi (60)]; the majority of investigations showed no such relation [Parkes Weber, Allard and S. Weber, etc. (61)].

Of great importance is the fact, first pointed out by Kahler, that the Bence-Jones (62) albumin appears in myelomatosis—a disease peculiar to the medulla. The only apparent exceptions are the observations of Askanazy and Raschkes (63). In Askanazy's case there was probably also lymphæmia; moreover, as myeloma sometimes stimulates leuchæmia, it is possible that such was the case here. Raschkes' case was nominally one of severe osteomalacia, but it is possible that here too it was in reality a question of myelomatosis.

F.—ON THE PATHOGENESIS OF OSTEOMALACIA AND RICKETS.

In all discussions on the origin of osteomalacia and rickets local changes in the skeleton occupy the most prominent position. Clinical experience, however, shows that essential characteristics of the disease are also to be found elsewhere. In the majority of cases other parts (muscle, nerves) are also attacked, and frequently the metamorphosis of the bone is not even of the first importance from the symptomatic standpoint. Hypotheses which ignore this fact can therefore lay little claim for consideration.

Hence it follows that the view that a primary lack of calcium is the origin of osteomalacia and rachitis is not satisfactory, whether it be assumed in the unsuitable nature of the food—calcium and sodium chloride deficit [Seeman, Zander, Zweifel (64)]; in defective resorption of calcium—lack of HCl in the stomach [Seeman, Zweifel (64)]; in disturbance of the function of the intestines, in abnormal loss of calcium through the action of unusual acids in the blood or bone—lactic and carbonic acid from the inflamed medulla [Pommer, Rindfleisch, Wachsmuth (65)]; or in the increased

calcium consumption during either sufficient or insufficient calcium intake—puerperal ostcomalacia. All these hypotheses break down before the actual fact that not a single one of these possibilities—if they ever occur at all—can be exhibited in a growing or adult person in such degree as to bring about adequate pathological effects. The reference to clinical and experimental discoveries in veterinary pathology, according to which the administration of food containing no calcium, or the administration of lactic acid, produced rachitic or osteomalacial metamorphoses in the bone (66), does not increase the value of the above theories, for it has not once been proved that the fragility of the bones, which appeared spontaneously in the animals tested, is based on lack of calcium in the food, or on the action of acids [Heiss (66)]. Moreover, in the majority of cases, this fragility has been experimentally caused, and is neither ostcomalacia nor rickets, but osteoporosis (67); only in the experiment of Voit (68) was bone metamorphosis demonstrated (von Buhl] resembling that caused by rachitis in mankind. However, in this seemingly convincing experiment the quantitative content of calcium in the organism of the rachitic animal differs from that observed in the rachitic child. While in experimental rachitis there is a reduction, absolute and relative, in the calcium contained in the bones and flesh, in the rachitic child the absolute content of calcium in the bones is smaller, but that of the flesh greater [Brubacher (69)]—in any case not less than in the normal state [W. Stöltzner (70)].

The question now is, How is it that the rachitic bone fails to assimilate calcium in spite of sufficient being present in tissues and blood? The answer can only be that the cells of the osteogenic tissue have so changed in their fundamental biological character as to have lost the capacity for absorbing and assimilating calcium (71).

The incapacity of the cells of rachitic bone to assimilate calcium, and that of the osteomalacial to retain calcium, has been traced to an abnormal function of those organs which are regarded as influencing both bone formation and metabolism. In rachitis the thymus [Friedleben, von Mettenheimer, Basch (72), etc.], the suprarenal glands [Stöltzner (73)], and the thyroid [O. Heubner (74), etc.], were taken into account. In osteomalacia the thyroid gland [Hönnicke] and the ovaries have been discussed in turn [Fehling]. This view of the matter certainly fulfils all the requirements of the above-mentioned claim—viz., that all theories of this disease must explain not only the condition of the skeleton, but also that of the organs. It is well known that the glands just mentioned have a certain influence on the chemical processes in the body, even though no detailed proof exists.

Further research on the essential nature of rachitis was impossible in this direction. The results of experiments on the relation of the thymus to the metabolism of calcium are somewhat contradictory (75). Therapeutic successes from the administration of thymus are lacking [W. Stöltzner and W. Lissauer (76)], as are also those from thyroid gland [O. Heubner, W. Knöpfelmacher] and suprarenal gland administration [L. Langstein, Neter, Hönigsberger (77)]. Bossi, however, claims to have produced considerable improvement in the condition of the bones

in osteomalacia by the injection of ½ centigramme of 1 per cent. adrenalin solution daily for five days.

The theory which connects osteomalacia with an abnormal function of the genital glands appears well founded, though even here too many uncertainties arise. One fact seems established—viz., that the removal of the genital glands (with or without the uterus) results in the cure of osteomalacia [Fehling, etc.]; and, further, it is certain that during pregnancy and parturition a direct "physiological" osteomalacia of the pelvic bone takes place [Hanau (78)]. But as soon as the experiment is questioned doubts spring up (79). According to the experiments hitherto made, it cannot with certainty be affirmed that castration affects the metabolism of phosphorus, calcium, and magnesia; nor have those experiments uniform results which deal with the effect of ovarin preparations on the metabolism of these elements in the castrated and in the normal organism. The effect of castration on the metabolism of calcium and phosphorus appears more lasting in female osteomalacia patients.

S. Neumann, Goldthwait, Painter, Osgood, and Crudden have observed increase of calx and phosphorus after castration (*vide* Table, pp. 1264, 1265). But, as I have already said, I hesitate to accept the explanation of a new formation of bone being here involved. In Neumann's cases, as well as in other investigations, increase of calcium and phosphoric acid occurs even in a severe stage of the disease, and in the investigations of Sauerbruch and Hotz the same result was obtained through the administration of phosphorus. The successes of organic therapeutics with ovarian substance are only of negative value [von Korczynski, Senator]. The same holds good of the action of the thyroid gland substance [Hotz, Senator], which is of value in forming an opinion on the theory recently brought forward by Hönnicke that osteomalacia is the result of disease of the thyroid gland. We must therefore be content for the present with a *non libuet*.

Chalmers Watson has conducted a series of investigations, the results of which show that the bones of animals fed on an excessive meat diet present an appearance of delayed and imperfect ossification with increased vascularity, and an increase in the number of red blood-corpuscles (82). To the naked eye the changes closely simulate those present in advanced cases of rickets in the human subject, but under the microscope they appear quite distinct from those present in that disease.

LITERATURE.

1. Fehling: Ueber Wesen und Behandl. der puerperalen Osteomalazie. Ar. Gy. **39.** 182. 1890.

2. Hoennicke: Ueber das Wesen der Osteomalazie, etc. 1905.

3. Neumann: Über die Stoffwechselverhält. des Kalziums, etc., bei puerp. Osteomalazie, etc. Ar. Gy. **51.** 130 ff. 1896.

4. Limbeck: Zur Kenntnis der Osteomalazie. W. m. W. **1894.** 738, 794, 843.—v. Korczynski: Zur Kennt. des Stoffw. bei Osteomalazie. W. m. P. **1902.** 10. 72.

5. R. v. Limbeck: l. c. Nr. 4.

6. Neumann: l. c. Nr. 3.

7. v. Korczynski: l. c. Nr. 4.

8. Beck: Ueber des gegenseitige Verhält. der N-haltigen Substanzen im Harn bei Osteomalazie. P. W. **1894.** 42.

9. Segelken: Ueber multiples Myelom und Stoffwechselunters. bei demselben. D. Ar. M. **58.** 276. 1896.

9a. Johannessen: Chron. Gelenkrheumat. und Arthritis deform. im Kindesalter. Z. M. **39.** 313. 1899.

10. A General Summary of the Chemical Analysis of Osteomalacial Bones, by M. Levy. Chem. Untersuch. über den osteomal. Knochen. Z. p. C. **19.** 239. 1894.

11. Galimard u. König: Über die Analyse der Knochen in Osteomal. infant. In Pharm. Chem. **21.** 352-357. Ref. Chem. Ctb. **1905.** 1332.

12. Mörs u. Muck: Beitr. zur Kenntnis der Osteomalazie. D. Ar. M. **5.** 485. 1869.

13. C. Schmidt: An. c. P. **61.** 329. 1847.

14. Friedleben: Beitr. zur Kenntnis der physikal. und chem. Konstitution wachsender und rachitis. Knochen der ersten Kindheit. Ja. K. **3.** 163.

15. Schmidt: l. c. Nr. 13.—Weber: Zur Kennt. der Osteomalazie insbes. der senilen und über das Vorkom. von Milchsäure im osteomal. Knochen. Ar. p. A. **38.** 1.—Drivon, cit. by A. Senator: Osteomalazie, in Ziemssen's Handb. Bd. 13a. 200. 1875.—Mörs u. Muck: l. c. Nr. 12.—Steiner: Ueber die pathol.-anat. Veränderungen bei Osteomalazie. Diss. Zurich, 1869.

16. Langendorff u. Mommsen: Zur Kenntnis der Osteomalacie. Ar. p. A. **69.** 452. 1877.—Levy: l. c. Nr. 10.

17. Levy: l. c. Nr. 10.

18. Gusserow: Mo. G. G. **20.** 19.

19. Pagenstecher: Ibid. **19.** 111.

20. Bouley u. Hanot, cit. by Levy: l. c. Nr. 10.—Langendorff u. Mommsen: l. c. Nr. 16.—Wulf, cit. by Levy, l. c. Nr. 10.

21. Höxter: Beitr. zur quant. Harnanalyse bei Osteomalazie. Diss. Würzb., 1888.—Warschauer: Diss. Würzb., 1890.—Fehling: l. c. Nr. 1.—Langendorff u. Mommsen: l. c. Nr. 16.

22. R. v. Limbeck: l. c. Nr. 4.—S. Neumann: l. c. Nr. 3.—v. Korczynski: l. c. Nr. 4.—Sauerbruch: Ein Beitr. zum Stoffwech. des Kalks und der Phosphorsäure bei infant. Osteomalazie. Diss. Leipzig, 1902.—Goldthwait, Painter, Osgood and McCrudden: On the Metabolism of Osteomalacia. A. J. P. **14.** 389-402. 1905. (The tables for Ca, P_2O_5, cit. after Hotz.)—G. Hotz: Phosphorsäure- und Kalkstoffwech. bei Osteomalazie unter dem Einfl. der Phosphorsäure. Z. e. P. **3.** 606. 1906.

23. Senator: Zur Kennt. der Osteomalazie und der Organther. B. k. W. **1897.** 109.

24. de Coninck: Ar. g. m. **1895.** 374.—Chabrié: C. r. S. B. **1895.** Sept.

25. Vierordt: Rachitis, in Nothnagel's Handb. **7.** 2. 21.

26. Brubacher: Ueber den Gehalt an anorgan. Stoffen, besonders an Kalk, in den Knochen und Organen norm. und rachit. Kinder. Z. B. **27.** 517.

27. Brubacher: l. c. Nr. 26. 546.—Stöltzner: Die Stellung des Kalks in der Pathol. der Rachitis. Ja. K. **50.** 268. (Literature.)

28. Rüdel: Ueber die Resorp. und die Aussch. der Kalksalze bei rachit. Kindern. E. A. **33.** 90. 1894.—Seemann: Zur Pathogen. und Aetiol. der Rachitis. Ar. p. A. **77.** 309. 1879.—Baginsky: Zur Pathol. der Rachitis. Ibid. **87.** 301. 1882.—Fischl: Pathogen. der Rachitis. Ar. K. **31.** 1901. (Literature.)

29. Zweifel: Aetiol. Prophylaxis u. Ther. der Rachitis. 1900. 179.

30. Forster: Kalkbedarf des Kindes. Mitt. aus der Münch. morph. u. phys. Ges. Nr. 3. 6 März. 1886.

31. Drachmann, Stokvis, cit. by Pribram: l. c. Nr. 34.

32. C. v. Noorden u. Belgardt: Zur Pathol. des Kalkstoffw. B. k. W. **1894.**

33. Johannessen: l. c. Nr. 9a. (Literature.)

34. Pribram: Chron. Gelenkrheum. u. Osteoarthr., in Nothnagel's Handb. **7.** 2. 79.

35. Limbeck: l. c. Nr. 4.—Korczynski: l. c. Nr. 4.—Neumann: l. c. Nr. 3.

36. Limbeck: l. c. Nr. 4.—Neumann: l. c. Nr. 3.—Korczynski: l. c. Nr. 4.—Sauerbruch: l. c. Nr. 22.—Hotz: l. c. Nr. 22.

37. Zweifel: l. c. Nr. 29.

38. R. v. Jaksch: Clin. Diagnosis.—Winckel-Eisenhardt: Beitr. zur Aetiol. der puerp. Osteomalazie. D. Ar. M. **49.** 182. 1892. (Literature.)

39. Schiff, cit. by Vierordt: l. c. Nr. 25. P. 72.—L. Morse: Ueber Blutuntersuch. bei Rachitis. Ja. K. **26.** 156.

40. Loos: Veränder. der morphol. Bestandteile des Blutes bei versch. Krankh. des Kindesalters. Ja. K. **39.** 331.—Vierordt: l. c. Nr. 25. P. 73.

41. v. Jaksch: Ueber die Alkaleszenz des Blutes. Z. M. **13.** 355. 1888.—Fehling: l. c. Nr. 1.—Eisenhardt: l. c. Nr. 38. 184.

42. Kobler: Zur Kennt. der Osteomalazie. W. k. W. **1888.** Nr. 22, 23.

43. Limbeck: l. c. Nr. 4.—Senator: l. c. Nr. 23.

44. Stöltzner: Bestim. der Blutalkaleszenz an rachit. und nichtrachit. Kindern. Ja. K. **45.** 29. 1897.

45. Albrecht u. Zdarek: Ueber den chem. Befund bei Ochronose der Knorpel. Z. H. **23.** 379. 1902.

46. Langstein: Zur Kenntnis der Ochronose. Be. P. P. **4.** 145; Zum Chemismus der Ochronose. B. k. W. **1906.** 597.

47. Pick: Ueber die Ochronose. B. k. W. **1906.** Nrs. 16-19. (Literature.)

48. Winckel: C. G. **1889.** 48.—Mörs u. Muck: l. c. Nr. 12.—Langendorff u. Mommsen: l. c. Nr. 16.—Kier: Virchow J. B. 1883. II. 606.—Hoffmann: Milchsäuregeh. des Harns bei Osteomalazie. C. i. M. **1897.** 329.

49. H. Bence-Jones: On a New Substance occurring in the Urine of a Patient with Mollities Ossium. P. T. **1848.** Part I. 55.

50. Dalrymple: On the Microscop. Character of Mollities Ossium. Dublin Quart. J. M. Sc. **1846.** Vol. II. 85.

51. For a summary of the Literature on Bence-Jones to 1903, see F. Parkes Weber: A Case of Multiple Myeloma (myelomatosis) with Bence-Jones Proteid in the Urine. M.-C. T. Vol. **86.** 1903.—Also Bertoge: Contrib. à l'étude de la maladie de Bence-Jones. Re. M. **1904.** 390. J. R. Charles: B. M. J. 1907. Vol. I. Herxheimer: Virchow's Archiv. 1905-6.

52. Bence-Jones: l. c. Nr. 49.—Huppert: Ein Fall von Albumosurie. P. W. **1889.** 33.—Kühne: Ueber Hemialbumose im Harn. Z. B. **19.** 209. 1883.

53. Magnus-Levy: Ueber den Bence-Jones' Eiweisskörper. Z. p. C. **30.** 200. 1900. (Literature.)

54. Abderhalden u. Rostoski: Beitr. zur Kenntnis des Bence-Jones' Eiweisskörpers. Z. p. C. **46.** 125. 1905.

55. Grutterink u. de Graaff: Ueber die Darstell. einer kristallinischen Harnalbumose. Z. p. C. **34.** 393. 1901. (Literature.)

56. Magnus-Levy: l. c. Nr. 53.

57. Parkes Weber, Hutchison, and Macleod: l. c. Nr. 51.

58. Ellinger: Das Vorkom. des Bence-Jones' Körpers im Harn bei Tumoren des Knochenmarkes und seine diag. Bedeut. D. Ar. M. **62.** 255. 1899.

59. Magnus-Levy: l. c. Nr. 53.

60. Voit u. Salvendi: Bence-Jones Albuminurie. Mü. m. W. **1904.** 29. 1281.

61. F. Parkes Weber: l. c. Nr. 51.—Allard u. Weber: Ueber die Beziehungen der Bence-Jones Albumosurie zum Eiweiss-stoffw. D. m. W. **1906.** 1251.—Grutterink u. de Graaff: l. c. Nr. 55.

62. Kahler: Zur Symptomatol. des multiplen Myeloms: Beobacht. von Albumosurie. P. W. **1889.** 33.

63. Raschkes: Ein Fall von seniler Osteomalazie mit Albumosurie. P. W. **1894.** 649.—Askanazy: Ueber die diagnost. Bedeut. der Aussch. des Bence-Jones' Körpers aus dem Harn. D. Ar. M. **68.** 34.

64. Seemann: l. c. Nr. 28.—Zander: Zur Lehre von der Aetiol., etc., der Rachitis. Ar. p. A. **83.** 379.—Zweifel: l. c. Nr. 29.

65. Pommer: Über Osteomalazie und Rachitis, etc. 1885. (Literature.)—Wachsmuth: Zur Theorie der Rachitis. Ja. K. **39.** 56. 1892. (Literature.)

66. Rüdel: l. c. Nr. 28.—Rey: Über Resorp. und Aussch. des Kalkes. D. m. W. **1895.** Nr. 35.—Vierordt: l. c. Nr. 25.—Stöltzner: l. c. Nr. 27.—Roloff: Ueber Osteomalazie und Rachitis. Ar. p. A. **37.** 455.—Stilling u. v. Mering: Ueber exper. Erzeugung von Osteomalazie. C. m. W. **1899.** 203.—Heiss: Kann man durch Einführung von Milchsäure in den Darm eines Tieres dem Knochen anorgan. Bestandteile entziehen? Z. B. **12.** 150 ff.—Siedamgrotzky u. Hofmeister: Die Einwirk. andauernder Milchsäureverabreichung auf die Knochen der Pflanzen-

fresser. C. m. W. **1879.** 792.—Baginsky: Zur Pathol. d. Rachitis. Ar. K. **3.** 2.—Voit: Ueber die Bedeut. des Kalks für den tier. Organismus. Z. B. **16.** 71.—Weiske: Ueber Knochenzusamm. bei versch. Ernährung. Z. B. **10.** 413.—Forster: Über die Bedeut. der Aschenbestandt. in der Nahrung. Z. B. **9.** 296. 1873.—Forster: Ueber die Verarmung des Körpers speziell der Knochen an Kalk bei ungenügender Kalkzufuhr. Z. B. **12.** 464.—Zweifel: l. c. Nr. 29. (Literature.)—Gelpke: Die Osteomalazie im Ergolzthal. 1891.—Troitzky: Die klin. und exper. englische Krankheit. Ja. K. **23.** 241. 1897. (Literature.)

67. Miwa u. Stöltzner: Ueber die bei jungen Hunden durch kalkarme Fütterung entstehende Knochenerkrankung. Be. A. P. **24.** 578. 1898.

68. Voit: l. c. Nr. 66.

69. Brubacher: l. c. Nr. 26.

70. Stöltzner: l. c. Nr. 27.

71. Vierordt: l. c. Nr. 25.—Brubacher: l. c.—Stöltzner: l. c. Nr. 27.—Pfaundler: Ueber die Elemente der Gewebsverkalkung und ihre Beziehung zur Rachitisfrage. Ja. K. **60.** 123.

72. Friedleben: Die Physiol. der Thymusdrüse, etc. 1858.—v. Mettenheimer: Zum Verhalt. der Thymusdrüse in Gesundheit u. Krankheit. Ja. K. 46. 1898.—Mendel: Thymusdrüse u. Rachitis. Mü. m. W. **1902.** Nr. 4.—Basch: Ueber Ausschaltung der Thymusdrüse. Verhandl. d. Deutsch. Ges. f. Kindk. 1903. 239; and W. k. W. **1903.** Nr. 31.

73. Stöltzner: Ueber Behandl. der Rachitis mit Nebennierensubstanz. Ja. K. **51.** 73, 199. 1900.

74. Heubner: Ueber einige Versuche der Anwend. des Schilddrüsensaftes bei Rachitis. B. k. W. **1896.** Nr. 31.—Knöpfelmacher: Ü. einige therap. Versuche mit Schilddrüsenfütterung. W. k. W. **1895.** Nr. 41.—Sinnhuber: Ueber die Beziehungen des Thymus zum Kalkstoffw. Z. M. **54.** 38. 1904.

75. Basch: l. c. Nr. 72; and F. Sinnhuber: l. c. Nr. 74.—Fischl: Über der Bedeut. der Thymusexstirpation bei jungen Tieren. Z. e. P. **1.** 388. (Literature.)

76. Stöltzner u. Lissauer: Ueber die Behandl. der Rachitis mit Thymussubstanz. Ja. K. **50.** 397. 1899.

77. Langstein: Ueber die Behandl. der Rachitis mit Nebennierensubstanz. Ja. K. **53.** 465. 1901.—Neter: Ueber die Behandl. der Rachitis, etc. Ibid. **52.** 601. 1900.—Hönigsberger: Zur Behandl. der Rachitis, etc. Mü. m. W. 1901. 627.

78. Hanau: F. M. **1892.**

79. General summary of the Literature by A. Magnus-Levy: This Book. **1.**

80. Hönnike: l. c. Nr. 2.

81. Bussi: Osteomalacia and the Suprarenal Capsule. Il Policlinico. Sez. prat. fasc. 1907.

82. Chalmers Watson: Influence of Excessive Meat Diet on the Osseous System. L. 1906. Dec. 8.

83. Hotz: Osteomalacia. Z. e. P. 1907. P. 604.

84. McCrudden: Influence of Castration upon the Metabolism in Osteomalacia. A. J. P. 1906. Bd. 17. P. 211.

CHAPTER XVIII

DIABETES INSIPIDUS

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Translated by A. L. Edwards.

A.—CONSUMPTION OF ENERGY IN DIABETES INSIPIDUS.

A. Magnus-Levy (1) found that a patient weighing 65½ kilogrammes had an oxygen consumption of 210 c.c. a minute, equal to 3·97 c.c. per kilogramme. This estimate is somewhat above normal.

As far as is known from recent investigations, the food requirements are, as a rule, normal.

Tallqvist reports a case where the patient's weight was 65 kilogrammes, the gross intake 43 calories per kilogramme, and the increase of weight in four weeks amounted to 2 kilogrammes. During another period of examination, when the food contained 39·1 calories per kilogramme, the weight sank from 66·8 to 62·2 kilogrammes. The decrease in weight is to be traced to loss of water, and for two reasons: First, because it took place simultaneously with retention of nitrogen; and, secondly, because, what was not the case in the former period, the diuresis increased owing to a higher percentage of albumin in the food. In another period of ten days' duration, with no albumin in the food and 40 calories per kilogramme, nitrogen remained stationary, but the patient lost 500 grammes.

With 43 calories per kilogramme of body-weight, and upon a diet poor in albumin, there was an increase of 3 kilogrammes in one month. Similar figures are given by other authorities [Vannini, Strubell, Hirschfeld, Gerhardt, Butler and French (3)].

This fully accords with clinical experience, which shows that, as a rule, the state of nutrition in diabetes insipidus undergoes no important change. In some cases, it is true, at the beginning of the disease a considerable loss of weight takes place, but this generally ceases after a short time. In other cases, again, in spite of an increase of food, emaciation sets in; only improvement in the polyuria can check this process.

Conclusions *a posteriori* on abnormal metabolic processes in diabetes insipidus must not be drawn from statements such as these, which abound in earlier literature. It is well known that serious errors can occur when considering nutrition solely with regard to its quality and quantity. In diabetes insipidus the primary cause of loss of weight lies in the loss of water, from which the patient suffers in the early stages of the disease.

Nevertheless, these estimates provide opportunity for looking the question in the face as to whether in diabetes insipidus there can be factors at work contributing a higher rate of exchange of energy.

In the first place, the fact must not be neglected that the diabetes is not generally an independent form of disease, but, according to its nature, etiology and clinical importance, a specially striking symptom common to diseases sometimes widely differing in character. Most probably in all cases the first cause of polyuria is to be found in either organic, or functional, injury to certain parts of the nervous system. The cause itself, however, may vary in nature, although it exercises a determining influence on the rate of oxidation—*e.g.*, diseases of the hypophysis cerebri, thyroid, etc. But these are disturbances co-ordinate with the diabetic syndrome, and not subordinate thereto.

The reaction of polyuria on the nitrogenous metabolism has been determined experimentally, and it has been found that an abnormal amount of water in the body leads to an increased output of nitrogen and nitrogen extractives (4). This fact is one that must be taken into consideration in diabetes insipidus. It is, nevertheless, improbable that this action of polyuria persists throughout the whole course of the disease, more especially as in the experiment it is of very short duration. [Oppenheim, von Noorden (5)]. It must, however, be remembered that what is true of the normal does not necessarily hold good in the case of the diseased organism, and it cannot be overlooked that in diabetes insipidus the abnormal amount of water present in the body produces an abnormal rate of nitrogenous metabolism.

In another direction polyuria is of importance for the general metabolism. The excessive quantity of fluid absorbed and later discharged in the urine demands so great an expenditure of heat in order to keep it at the temperature of the blood that changes in the economy of heat are thereby brought about. For instance, to bring 10 litres of water from 15° C. up to blood-heat (37° C.) an expenditure of 220 calories is required [von Noorden (6)]; an expenditure of 2,000 calories, which would be the amount for a patient weighing 50 kilogrammes, amounts to 11 per cent. of the total heat produced.

It is quite possible that the somewhat high figure for oxygen consumption in Magnus-Levy's patient may be traced to this. As a rule, the extra demand for heat thus rendered necessary is not of great importance; relatively it is higher when the absolute requirement is small than when this is great. It is, however, open to question whether this factor is of any value, for this excess of heat which disappears with the urine can be balanced by restricting the loss of heat through the skin (evaporation, conduction, and radiation). Indeed, in diabetes insipidus a reduction in the temperature of the skin (axilla) is frequently observed.

B.—METABOLISM OF PROTEIN.

The metabolism of protein has aroused special interest for a considerable time—in fact, ever since the fluctuations of the urea output in diabetes insipidus were made known. This may be normal, low, or very high. Hence the conclusion that cases of diabetes insipidus may be characterized by increased disintegration of protoplasm [azoturia (7)]. But, of course, a high urea output is not synonymous with abnormal breaking down of protein. The amount of urea depends first of all on the proportion of albumin present in the food, and there is nothing in the investigations reported in the earlier literature to show that any other factors are at work having an injurious effect on the protoplasm in diabetes. No figures relative to the nitrogenous balance exist; at best, parallels of little or no value have been made by comparison with the urea output of normal persons on the same diet.

Only recently have exhaustive investigations given the nitrogen input and output. They go to prove, however, that, as a rule, the albumin metabolism in the diabetic patient is not affected. The patient, with a sufficient supply of calories and a medium or low supply of nitrogen, maintains precisely the same protein balance as a normal person [Strubell, Tallqvist, Vannini, Gerhardt, Butler and French (8)]. Isolated observations report, it is true, loss of albumin, in spite of a diet of apparently sufficient calorific and protein values. The loss of nitrogen is generally slight—hardly more than 2 grammes in twenty-four hours [Strubell, Vannini, Hirschfeld, Ferranini (9)].

Hence the conclusion either that the action of augmented quantities of fluid was injurious to protoplasm (which is improbable), or that the diet was deficient in calories. On a close observation of the cases neither inference is very probable. Polyuria is in every case by no means abnormally high—on the whole, much lower than in other investigations, where, after several weeks of observation, no increase in loss of albumin could be shown—*e.g.*, Butler and French (10). The intake of calories is likewise not abnormally low. The figures for patients at rest are as follows: Strubell, 40·62 (gross) calories; Vannini, 37·5 (nett) calories; Hirschfeld, about 44 (gross) calories. It must also be borne in mind that in all these cases the fundamental disease was not necessarily particularly severe, or one directly influencing the albumin metabolism. All the patients suffered apparently from the so-called idiopathic form of diabetes insipidus.

I consider it far more probable that the abnormal excretion of nitrogen in the above-mentioned cases was an after-effect of the previous diet and the fluctuating supply of fluid. The experiments are generally of short duration—*e.g.*, Strubell, five days; Vannini, four days.

A previous plentiful supply of albumin or of fluid, or reduction of water, could quite well, even in five days, have some influence on the nitrogen output. Up to the present, then, the investigations made are of no value in deciding the important question whether cases of diabetes insipidus exist with pathological loss of protoplasm. This

can only be decided by a series of investigations covering a considerable period. Seiler's (47) recent work showed a normal output of nitrogen with a free water intake (7 litres urine), and a 50 per cent. diminished nitrogen excretion when the water intake was restricted (3 litres of urine).

C.—WATER ECONOMY.

The metabolism of water in diabetes insipidus exhibits a number of important peculiarities. The water intake and output are much increased. Many things respecting the quantity and periods of the discharge of urine, as well as the peculiarity of its secretion by the kidneys, go to prove that here polyuria is primary, polydipsia secondary.

The diabetic patient excretes more urine than a normal person, not only in consequence of his drinking more, for with a partial or even complete suppression of fluid in the diet the secretion of urine continues for a considerable time, though perhaps diminished in quantity. But in this matter patients vary. Sometimes the secretion of urine ceases from the moment the intake is diminished. In such cases there is no important loss of water in the tissues. In others, again, the secretion of urine is considerable for long periods, only ceasing temporarily for short intervals. In a case of Strubell's the secretion of urine only ceased (and then for merely an hour and a half) after the patient had abstained from drinking for thirty-six hours. Such patients lose considerable quantities of water from the tissues, and as a direct consequence thereof the concentration of the tissue fluids is altered, and the onset of grave symptoms in connection with the heart and nervous system is precipitated.

Needless to say, a steady loss of water from the organs and fluids of the body is incompatible with the continuance of the processes of life. Under such circumstances, speedy death would be inevitable. In reality, loss of water in the tissues is a temporary phase of diabetes insipidus, and probably only the accompaniment of the enforced diminution or total withdrawal of water. If thirst be freely satisfied, the water lost (in a minority of cases) represents that contained in the diet, together with the fluids produced by its assimilation in the body ; but far more frequently the loss is not so great. Therefore, as a rule, there is no danger of excessive dryness of the tissues in diabetic patients (see below, Blood). The increase of thirst, and its satisfaction, is manifestly the most essential and potent regulator in protecting the body from entire lack of water.

The discharge of water through the kidneys is, in diabetes insipidus, above the normal, not only absolutely, but also relatively to the total loss of water. Normally, whatever the amount of fluid assimilated, it is so distributed among the excretory tissues that between 66 per cent. and 70 per cent. of the entire water of the body is discharged through the kidneys, the rest being carried off through the lungs and skin (*perspiratio insensibilis*), whereas in the diabetic patient the proportion of urine to the total amount of water is, as a rule, far higher—sometimes even over

90 per cent. Hence the amount of water given off in evaporation is decidedly subnormal, not only in relative value to the total mass of water absorbed and later discharged in the urine, but also frequently in absolute value. But this latter is not always the case, and may even differ in the same patient at different times [Strauss, Bürger, Flatten, Strubell, Vannini (11)]. Moreover, the degree of *perspiratio insensibilis* is independent of the quantity of water absorbed [Flatten]; but, on the other hand, it seems sometimes dependent on diet. A. Pribram (12) has observed that on a carbohydrate rich diet it is greater than on a diet rich in albumin.

The reduction of *perspiratio insensibilis* can, of course, only affect that proportion of water which is evaporated through the skin, for the breath is always saturated with aqueous vapour. The patient is made aware of this reduction by his inability to perspire, this being one of the first and most troublesome symptoms. When very pronounced, it can even be synonymous with inability to regulate the internal temperature, so that a high external temperature or an increased production of heat causes a rise of the internal temperature [F. Stoermer (13)]. To these extremes the majority of patients are liable when the loss of water through skin and lungs can be increased by measures which in any case lead to an increase of evaporation—*e.g.*, vapour baths, cooling baths, fever, etc. At the same time, the apparently paradoxical fact is occasionally observed that, in spite of increased loss of water, the feeling of thirst decreases [Strubell, Meyer (14)].

Various abnormal peculiarities are noticeable regarding the periodicity of the urinary excretion. Differences are met with in the quantity of day and night discharge. Frequently the night urine is greater than that of the day, in spite of less fluid being assimilated; but this manifestation, like those mentioned above, is not regular. Almost as frequently the amount of the day and night urines is equal, or the former greater than the latter. But these details are nevertheless valuable, as they lend themselves so excellently to experimental illustration. Most diabetic patients respond to a supply of fluid—whether administered in one large or in several small quantities at short intervals—by a retarded discharge of the same in the urine.

The curve of the water secretion, in contrast to the normal, where the fluid is more quickly discharged, reaches its maximum later, maintains it for a considerable time, and extends it over a long period—[bradyuria (15)]. This peculiarity explains the fact that the quantity of the night urine is greater than that of the day urine.

But bradyuria is apparently not a distinctive feature of diabetes insipidus. Kraus, at least, found that the urine secretion curve took quite another course after an abundant supply of water—viz., a sharp rise and corresponding fall, more rapid discharge than under normal conditions and a subsequent minimum, which was maintained for a considerable time—tachyuria (16). It is, however, doubtful whether this mode of urinary excretion is peculiar to diabetes insipidus, for, besides the fact that up to the present this is the only case known, tachyuria is to be found under normal conditions [Strubell (17)].

The meaning of these facts is to be found in an abnormal action of the kidneys, an explanation long conjectured, but only recently more exhaustively investigated [Tallqvist, Meyer (18)].

The function of the normal kidney is to regulate the osmotic equilibrium of the fluids by the elimination of metabolic residues by means of two variable factors—the quantity and the concentration of the urine. These vary in value according to the number and nature of the urinary molecules. Under certain conditions they are either of equal or of diametrically opposite values—*e.g.*, the quantity as well as the concentration can increase when considerable quantities of salt or urea have to be removed from the body ; but generally in that case the concentration is increased rather than the quantity. It does not concern us at present by what mechanism the kidneys effect their purpose—whether by reabsorption of water in the tubules, or by active secretion of concentrated salt or urea solution. The fact remains that the kidneys in a normal state are able to prepare urine varying in concentration in accordance with the prevailing requirements, and solely by increasing the concentration to effect the discharge of solid elements without important increase in the quantity of urine. In diabetes insipidus the kidneys are clearly incapable of performing this duty, for the concentration of urine remains inconsiderable even under conditions where normally the kidneys react in very marked degree by increasing the osmotic tension of the urine—*e.g.*, on a diet containing much albumin and salt. But in diabetes insipidus these circumstances, as shown by numerous experiments, only cause an excessive increase of the quantity of urine (19).

The cause of this peculiar manifestation does not lie in a functional weakness of the diabetic kidneys, for the number of molecules discharged in the urine in twenty-four hours is the same for a diabetic patient as for a healthy person on the same diet—that is to say, in this direction the kidneys act quite normally. If it be desired to characterize more exactly the functional disturbance, it can only be said that the diabetic kidney is incapable of preparing concentrated urine. Accordingly, polyuria is to a certain extent a compensatory process and a means of hindering the retention of urinary material. This view gives a direct answer to the much-discussed question whether polyuria or polydipsia be the primary symptom in diabetes insipidus.

In diabetes insipidus there can be no doubt that polyuria is of primary importance. Since the kidneys can only discharge solid matter when abundantly diluted, the imminent danger of total loss of water must be obviated by ample supply of water in the diet. Accordingly, diabetes insipidus is based upon an abnormal action of the kidneys, probably due to nervous affection. The diabetic kidney has, however, not quite lost the power of concentrating urine, for in isolated cases it frequently asserts itself. But in comparison with the function of the normal kidney, it is certainly considerably deteriorated. Certain measures—*e.g.*, sudorifics, vapour baths, etc.—for drawing off in other ways the water that should be discharged by the kidneys bring this capacity into prominence again. According to many authorities, fever also causes a reduction in

the quantity and an increase in the osmotic concentration of the urine [A. Pribram, E. Pribram, Strubell, E. Meyer, H. Strauss]. Probably antipyrin, so often employed in the treatment of diabetes insipidus, acts in the same way [Hirschfeld (20)].

D.—THE DIGESTIVE ORGANS.

Increased secretion of *saliva* has been frequently observed (21). In Külz's case several hundred cubic centimetres of saliva were secreted daily. It may be assumed that polyuria and salivation originate in the same disturbance of the nervous system. Eckhard, in his experiments on polyuria, observed augmentation of submaxillary saliva. Careful investigations of the secretion in the intestinal canal have not been reported.

The *appetite* is not the same in all cases. Many patients experience no change, but in others there is an increase of appetite as well as of thirst, and these latter probably suffer from " azoturia."

Obstipation frequently occurs, probably from the great resorption of water from the intestines. The fæces contain, therefore, very little water as a rule, but show an increase of moisture when the discharge of water from the kidneys is drawn off by other means—*e.g.*, when polyuria is reduced by means of antipyrin [Hirschfeld].

The *absorption* of food is normal [Strubell, Vannini].

The following table gives the figures for the daily percentage of loss in the fæces :

Case.	*Author.*	*Duration of Experiment.*	*Percentage of Loss in Fæces.*			
			Dry Substance.	Nitrogen.	Fat.	Carbohydrate.
		Days.				
1	Strubell	11	—	8·33	—	—
2	Strubell	5	—	10·36	—	—
1	Vannini	6	5·05	8·21	6·51	0·968
2	Vannini	4	6·05	5·58	7·00	0·630
	Butler and French	34	—	10·90	—	—

E.—PERSPIRATION.

This subject has been already discussed above. It need only be mentioned here that Strauss (22) found higher osmotic concentration and greater content of salt in the perspiration than in the urine ($\Delta = -0{\cdot}40 = NaCl = 0{\cdot}41$ per cent.). This is exactly the reverse of the normal state, where the freezing-point of the urine is invariably higher than that of the perspiration.

F.—BLOOD.

The *specific gravity* of the blood is, as a rule, but little, if at all, increased (23). In Stoermer's case the specific gravity of the entire blood was 1066. Strubell (24) found a normal figure, as did also Gerhardt (1055) (25) and Strauss (1056, 1058, and 1060) (26). The specific gravity of the serum amounted to 1026 in Strauss's case, 1028 in Hocke's case (27).

The *osmotic concentration* of the blood has been frequently determined (28). The following table contains the figures obtained, together with the corresponding Δ values for the urine :

Author.	*δ Blood.*	*Δ Urine.*
Loeper	−0·51°	−0·37°
	−0·59°	−0·37°
	−0·59°	−0·41°
Hocke	−0·49°	−0·20°
	−0·52°	−0·33°
H. Strauss	−0·57°	—
E. Meyer	−0·56°	—

The *dry residue* of the blood is generally normal [Strubell (29)], in some cases reaching a high figure when there has been unlimited supply of fluid. Strauss (30) found 22·21 and 22·063 per cent., Meyer (31) 21·30 per cent. On limiting the supply of fluid, Strubell (29) found 23·24 and 23·26 per cent. Here evidently serious general disturbances made themselves felt. The increase of the dry residue is shown by higher proportions of *hæmoglobin* and *erythrocytes* [Meyer]. Geigel (32), on the other hand, observed a reduction of erythrocytes.

Strauss (33) has further conducted refractometrical investigations of blood, and gives figures very near the normal maximum.

G.—URINE.

1. Quality.

The most essential points have been discussed above, under Water (p. 1282).

2. Nitrogenous Constituents.

Vannini (34), in one case, gives for the urea 86·10 per cent., in another 90·66 per cent. Butler and French (35) found 94·96 per cent. Von Jaksch alone gives remarkable figures for urea nitrogen and amino-acid nitrogen. More than half the entire nitrogen is stated to have been excreted as amino-acid nitrogen. The figures for uric acid, contrary to former statements, were found normal (37), as were also those for ammonia and extractives (37).

3. Chloride of Sodium.

In the earlier literature it is stated that the chloride output is increased in diabetes insipidus, but it has never been proved that this increase is due to anything but the salt contained in the diet [Oppenheim (38)]. Ferranini recently reported two cases in which an increased chloride excretion formed the distinguishing feature. Vannini and Ascoli, who paid special attention to the chloride content of the food, found a normal output.

4. Sulphates and Ethereal Sulphates.

The excretion of sulphates runs parallel with that of the albumin disintegration. The values for the ethereal sulphates are normal (40).

5. Phosphates.

Vannini observed (with a negative nitrogen balance) a loss of 0·529 gramme in an experiment extending over four days.

6. Sugar.

In diabetes insipidus sugar is, of course, not present; but in some cases sugar has been observed, and has been attributed to a " remainder " from diabetes mellitus.

Alimentary glycosuria has sometimes been found, sometimes not (42, 43, 49).

7. Inosit.

This substance has often been met with in the urine from cases of diabetes insipidus (44). At first great stress was laid upon the fact, but as it is not uniformly present in cases of diabetes, and may also occur in the urine of other diseases, as well as in healthy urine after excessive intake of fluids, it is not now regarded as important.

8. Dextrins.

Alfthan has investigated two cases, but has not found any marked deviation from the normal.

LITERATURE.

1. Magnus-Levy: Respirationsvers. an Diabetikern. Z. M. **56.** 1905.
2. Tallqvist: Z. M. **49.** 181. 1903.
3. Vannini: Ueber den Stoffwech. bei Diab. insipidus. B. k. W. **1900.** 638. —Strubell: Ueber Diab. insipidus. D. Ar. M. **62.** 89. 1899.—Hirschfeld:

Ueber den Stoffwech. im Diab. insipidus. Festschr. f. Salkowski, Beitr. z. wissensch. Med. u. Chem. **1904.** 187.—GERHARDT: Diab. insipidus. Nothnagel's Handb. 1899. **7.** 1. 14.—BUTLER AND FRENCH: On the Metabolism of a Patient suffering from Diabetes Insip., etc. Gu. H. Rep. **57.** 133. 1904.

4. MAGNUS-LEVY: This Book. Vol. I.

5. OPPENHEIM: Physiol. und Pathol. der Harnstoffaussch. Ar. P. M. **23.** 446. 1881.—v. NOORDEN: Path. d. Stoffw. **1893.** 143.

6. C. v. NOORDEN: l. c. Nr. 5.

7. Literature quoted by GERHARDT: l. c. Nr. 3, p. 10.

8. STRUBELL: l. c. Nr. 3.—TALLQVIST: l. c. Nr. 2.—VANNINI: l. c. Nr. 3.—GERHARDT: l. c. Nr. 3.—BUTLER AND FRENCH: l. c. Nr. 3.

9. STRUBELL: l. c. Nr. 3.—VANNINI: l. c. Nr. 3.—HIRSCHFELD: l. c. Nr. 3.—FERRANINI: Il diab. insipido come anomalia del ricambio. P. **9.** Abstr. in Jb. L. M. **1902.** 2. 52.

10. BUTLER AND FRENCH: l. c. Nr. 3.

11. STRAUSS: Ueber den Diab. insipidus. Diss. Tübing., 1870.—FLATTEN: Beitr. zur Pathogen. des Diab. insipidus. Ar. P. N. **13.** 682.—BÜRGER: Ueber die Perspiratio insen. bei Diab. mell. und insipidus. D. Ar. M. **11.** 323.—STRUBELL: l. c. Nr. 3.—VANNINI: l. c. Nr. 3.

12. PRIBRAM: P. W. **1871.** 1-38.

13. STOERMER: Diss. Kiel, 1892.

14. STRUBELL: l. c. Nr. 3.—MEYER: Ueber Diab. insipidus und andere Polyurien. D. Ar. M. **83.** 4. 1905.

15. FALCK: D. K. **1853.** Nrs. 41-43.—NEUSCHLER: Diss. Tübing., 1861.—PRIBRAM: l. c. Nr. 12.—PRIBRAM: Klin. Beobacht. bei zehn Fällen von Diab. insipidus. D. Ar. M. **76.** 198. 1903.—STRUBELL: l. c. Nr. 3.

16. KRAUS: Ein Beitr. zur Symptomat. des Diab. insipidus. Z. H. **8.** 432. 1887.

17. STRUBELL: l. c. Nr. 3.

18. TALLQVIST: l. c. Nr. 2.—MEYER: l. c. Nr. 14.

19. PRIBRAM: l. c. Nr. 12.—TALLQVIST: l. c. Nr. 2.—MEYER: l. c. Nr. 14.

20. HIRSCHFELD: l. c. Nr. 3.

21. KÜLZ: Path. u. Ther. des Diab. mellit. u. insipid. 2. 1875.

22. STRAUSS: Zur Kennt. des Wasserstoffwech. bei Diab. insip. Z. e. P. **1.** 408. 1905.

23. STRAUSS: l. c. Nr. 11.—STOERMER: Diss. Kiel, 1892.

24. STRUBELL: l. c. Nr. 3.

25. GERHARDT: l. c. Nr. 3.

26. STRAUSS: l. c. Nr. 22.

27. HOCKE: Beitr. zur Kennt. der Diab. insip. Mü. m. W. **1902.** 1817.

28. LOEPER: Du mecanisme regulateur de la composit. du sang. 1903.—HOCKE: l. c. Nr. 27.—STRAUSS: l. c. Nr. 22. 414.—MEYER: l. c. Nr. 14.

29. STRUBELL: l. c. Nr. 3.

30. STRAUSS: l. c. Nr. 11.

31. MEYER: l. c. Nr. 14.

32. GEIGEL: Beitr. zur Lehre vom Diab. insip. D. Ar. M. **37.** 55.

33. STRAUSS: l. c. Nr. 22. 415.

34. VANNINI: l. c. Nr. 3. 640.

35. BUTLER AND FRENCH: l. c. Nr. 3. 161.

36. R. v. JAKSCH: Ueber die Mischung der N-haltigen Bestandteile im Harn. Z. M. **47.** 46.

37. SENATOR: Diab. insip. ZIEMSSEN's Handb. **13A.** 270. 1876. (Literature.)—BUTLER AND FRENCH: l. c. Nr. 3. P. 166.—VANNINI: l. c. Nr. 3. 640.

38. OPPENHEIM: Kasuistis. Beitr. zur Polyurie. Z. M. **5.** 618. 1892.—Weiterer Beitr. zur Polyurie. **6.** 256. 1883.

39. FERRANINI: l. c. Nr. 9.

40. VANNINI: l. c. Nr. 3. 639.

41. SENATOR: l. c. Nr. 37. 271.

42. F. KRAUS: l. c. Nr. 16.—v. OORDT: Aliment. Glykosurie bei Krankh. des Nervensystems. Mü. m. W. **1898.** 2.

43. MORITZ: Aliment. Glykosurie. Mü. m. W. **1891.** 311.—KRAUS AND LUDWIG: Klin. Beitr. zur aliment. Glykosurie. W. k. W. **1891.** 899.

44. Mosler: Ueber Harnanaly. bei Diab. insip. Ar. p. A. 43. 229; 44. 44.—Strauss: l. c. Nr. 12.—Ebstein: Ueber die Beziehungen des Diab. insip. zu Erkrankungen des Nervensyst. D. Ar. M. 11. 344.—Külz: l. c. Nr. 21.—Pauli: Diss. Zürich, 1891.—McIlraith: Notes on Some Cases of Diab. Insip., etc. L. 2. 767. 1892.

45. Strauss: l. c. Nr. 11.—Külz: l. c. Nr. 21.

46. K. v. Alfthan: Ueber das tier. Gummi Landwehr's bei Diab. insip. B. k. W. 1902. Nr. 8.

47. Seiler: Diabetes Insipidus. Z. M. 1907. Bd. 61.

APPENDIX

ANALYSES AND CALORIFIC VALUES OF THE COMMONER FOOD-STUFFS

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The following data are included on account of their utility for clinical work. In some cases they cannot be considered more than approximate, but they may be confidently employed for the preparation of dietaries for the sick. When research investigations are carried out, it is usual to analyze separately the food used in each experiment. The composition, etc., of some of the generally used "artificial" foods is also given.

	Protein $N \times 6{\cdot}25$.	*Fat or Ether Extract.*	*Carbo-hydrates.*	*Mineral Matter.*	*Calories in* 100 *Grammes.*	*Calories in* 1 *Ounce.*
ANIMAL FOODS.						
Meats.						
Cooked :						
Beef (rump), boiled	34·10	7·50	—	1·10	209·5	65·3
Beef, roasted ..	34·20	8·20	—	1·40	216·0	61·7
Beef (round), boiled	32·80	12·50	—	0·90	250·6	71·7
Mutton, roasted ..	29·00	26·80	—	1·90	358·6	102·5
Mutton (leg), roasted	25·00	22·60	—	0·70	307·1	88·7
Mutton (leg), boiled	25·00	20·70	—	0·80	295·0	84·3
Veal (cutlets) ..	29·00	11·90	—	1·40	230·6	66·0
Veal, roasted ..	32·20	11·40	—	1·60	237·9	68·0
Lamb, roasted ..	24·60	11·90	—	1·60	212·0	60·6
Pork, roasted ..	32·60	19·70	—	1·80	316·8	90·6
Ham, smoked and boiled	20·20	22·40	—	6·10	299·1	82·5
Bacon (ribs) ..	24·80	37·60	—	2·20	469·3	128·5
Uncooked :						
Beef (rump) ..	1·23	22·50	4·50	—	134·1	38·2
Mutton (leg) ..	1·00	18·70	17·50	—	277·6	68·0
Veal (cutlets) ..	1·15	20·20	6·40	—	142·3	40·6
Lamb (leg)	1·00	18·60	22·60	—	286·3	81·5
Pork	0·80	14·10	25·50	—	294·9	84·0
Ham, smoked ..	4·70	16·50	38·80	—	428·4	125·5
Bacon	5·10	10·50	64·80	—	645·6	183·2
Kidney (sheep) ..	1·30	16·80	3·20	—	95·3	27·2
Liver (calf) ..	1·70	20·70	4·50	—	126·6	28·8
Tripe	0·50	16·40	8·50	—	147·8	42·3
Sweetbreads ..	16·80	12·10	—	1·60	181·3	51·7
Tongue	17·10	18·10	—	1·00	238·4	68·0

	Protein $N \times 6{\cdot}25$.	*Fat or Ether Extract.*	*Carbo-hydrates.*	*Mineral Matter.*	*Calories in* 100 *Grammes.*	*Calories in* 1 *Ounce.*
ANIMAL FOODS.						
Poultry and Game.						
COOKED :						
Chicken, fricassed ..	17·60	11·50	2·40	1·00	179·0	54·5
Turkey, roasted ..	27·80	18·40	—	1·20	285·1	81·4
UNCOOKED :						
Chicken	21·50	2·50	—	1·10	111·4	32·2
Goose	16·30	36·20	—	0·80	403·4	118·7
Turkey	21·10	22·90	—	1·00	299·4	85·0
Wild-duck	22·00	3·00	—	1·00	102·6	33·1
Pigeon	19·50	0·90	—	1·10	80·7	23·0
Hare	22·30	1·10	—	1·10	93·6	28·3
Rabbit	21·40	9·70	—	1·10	124·4	37·7
Sausages.						
Pork sausage ..	12·30	21·00	1·00	3·50	248·6	71·1
German sausage ..	16·40	17·90	15·00	4·50	251·9	72·0
Polony	17·20	32·60	2·30	2·80	383·1	109·0
Fish.						
COOKED (ALL BOILED):						
Herrings	26·40	9·90	—	2·20	199·1	56·8
Herrings (salt) ..	20·90	11·30	9·40	10·60	229·2	65·4
Sprat	14·00	6·60	2·40	1·50	128·5	53·1
Sardines	30·20	18·60	—	6·70	299·0	85·4
Salmon	19·60	10·20	5·10	1·70	193·9	55·4
Salmon, fresh ..	24·60	25·90	7·70	2·10	373·3	106·0
Trout	21·10	2·30	1·20	1·70	112·8	32·3
Lobster or crab, potted	14·80	24·80	—	4·90	162·9	49·3
Lobster or crab, tinned	18·10	1·10	—	0·60	81·8	21·5
Smelts	15·90	1·90	—	0·90	82·1	23·0
Salmon (Californian)	21·50	13·00	1·60	2·10	209·4	59·7
Eel	16·70	17·40	3·40	0·80	244·2	69·5
Red mullet ..	21·00	7·80	3·10	1·70	121·7	34·9
Roach	19·50	3·70	1·50	0·20	120·5	34·5
Gurnet	23·40	0·50	1·2	0·90	105·4	30·0
Mackerel	16·70	6·90	3·70	1·10	148·1	41·1
Tunny	24·10	11·20	—	2·00	197·1	56·3
Cod	21·70	0·30	1·50	0·70	97·8	28·1
Cod (salt)	21·00	0·20	1·90	3·94	95·6	28·0
Haddock	22·10	0·30	3·60	0·90	108·0	30·8
Hake	12·30	0·90	2·00	0·70	66·9	19·1
Whiting	16·90	0·40	3·70	0·40	88·5	25·1
Turbot	18·80	1·00	2·60	0·50	95·7	27·3
Brill	35·00	0·60	—	1·60	149·2	42·6
Halibut	20·30	4·00	—	1·00	120·4	34·5
Plaice	15·10	2·00	2·30	0·80	90·3	25·8
Sole	18·03	0·30	2·40	0·53	85·8	24·5
Lemon sole ..	15·30	2·80	3·20	0·96	103·1	29·4
Dory	17·50	0·40	2·50	0·20	85·7	24·4
UNCOOKED :						
Herrings	19·50	7·10	—	1·50	145·9	41·5
Herrings (salt) ..	18·90	16·90	—	14·50	234·5	66·9
Caviare	30·00	19·70	—	4·60	203·0	61·5
Salmon	15·00	9·50	—	0·90	149·8	37·5

	Protein $N \times 6{\cdot}25$.	*Fat or Ether Extract.*	*Carbo-hydrates.*	*Mineral Matter.*	*Calories. in 100 Grammes.*	*Calories in 1 Ounce.*
ANIMAL FOODS.						
Fish—UNCOOKED :						
Trout	19·20	2·10	—	1·20	98·2	28·0
Smelts	17·60	1·80	—	1·70	88·9	25·1
Salmon (Californian)	17·80	17·80	—	1·10	238·4	67·5
Eels	18·60	9·10	—	1·10	160·4	45·4
Red mullet ..	19·50	4·60	—	1·20	122·7	34·8
Mackerel	18·70	7·10	—	1·20	142·7	40·6
Cod	16·70	0·30	—	0·90	71·2	20·7
Cod, salt	27·30	0·30	—	19·00	114·6	30·6
Haddock	17·20	0·30	—	1·20	73·2	21·0
Hake	15·40	0·70	—	1·00	66·8	19·8
Whiting	15·10	0·40	—	(?)	65·6	18·7
Turbot	14·80	14·40	—	1·30	194·6	55·4
Halibut	18·60	5·20	—	1·00	124·6	35·5
Oysters	14·60	1·70	4·10	2·70	92·5	26·5
Turtle	19·80	0·50	—	1·20	85·7	24·5
VEGETABLE FOODS.						
Vegetables.						
COOKED :						
Potatoes boiled in skin	1·60	0·10	18·70	1·30	84·1	24·1
Potatoes boiled without skin	1·60	0·10	16·90	0·70	78·5	22·4
Scarlet runner ..	1·80	0·20	2·00	0·40	17·4	4·9
Cabbage, savoy ..	0·60	0·10	0·30	0·10	4·6	1·3
Beetroot	0·40	0·10	2·80	0·40	14·1	4·0
Salsify	1·20	0·10	8·10	0·60	39·1	11·1
Carrots	0·50	0·20	3·40	0·10	16·7	4·8
Vegetable marrow	0·10	—	0·10	0·10	0·8	0·2
Cauliflower ..	0·90	0·10	0·40	0·20	6·2	1·8
Onion	0·10	0·10	0·70	0·10	4·2	1·2
Parsnip	0·20	0·30	1·40	0·10	8·2	2·3
Jerusalem artichoke	1·80	0·10	4·60	0·60	27·1	7·7
Sea-kale	0·40	0·10	0·30	0·20	3·7	1·1
Broad beans ..	2·10	0·30	4·20	0·50	28·5	8·1
Turnip	0·30	0·10	0·60	0·30	4·6	1·3
Spinach	0·30	0·20	0·20	0·20	2·9	0·9
Green-pea	2·80	0·10	4·70	0·30	30·6	8·7
Broccoli	2·50	0·20	2·60	0·60	22·6	6·4
Brussels sprouts ..	2·80	0·10	4·30	0·50	30·1	8·6
Asparagus	2·10	0·10	2·10	0·70	18·1	5·2
Leeks	1·40	0·10	7·80	0·80	38·6	11·0
Green artichokes ..	2·90	0·20	7·70	1·10	45·3	12·9
Peas[1]	9·40	0·70	23·10	0·70	139·7	50·4
Haricot beans[1] ..	4·60	0·50	9·10	0·70	60·7	17·1
Lentils[1]	8·80	0·20	20·50	0·70	121·9	34·5
Petit pois	4·30	0·10	8·90	0·60	55·1	15·7
Baked beans ..	5·00	0·20	21·70	1·80	110·3	31·4
UNCOOKED :						
Cucumber	0·50	—	0·70	0·30	4·9	1·4
Radish	1·20	0·10	0·70	0·90	8·7	2·5
Lettuce	0·50	0·10	0·60	0·50	5·4	1·6
Celery	0·30	0·10	0·70	0·50	5·1	1·3
Tomato	1·00	0·20	0·10	0·70	6·3	1·8
Potato	2·10	0·10	24·40	0·70	109·5	31·0
Scarlet runner ..	2·30	0·30	7·40	0·80	42·4	12·0
Cabbage	1·50	0·50	5·80	1·20	34·5	9·8
Beetroot	1·60	0·10	9·70	1·10	47·2	13·3

[1] Bought dried.

	Protein N × 6·25.	*Fat or Ether Extract.*	*Carbo-hydrates.*	*Mineral Matter.*	*Calories in 100 Grammes.*	*Calories in 1 Ounce.*
VEGETABLE FOODS.						
Vegetables—UNCOOKED:						
Carrots	0·50	0·20	7·00	1·00	6·7	1·9
Vegetable marrow	0·60	0·20	2·60	0·50	14·8	4·2
Cauliflower	1·80	0·50	4·70	0·70	31·2	9·0
Onions	1·50	0·20	4·80	0·50	28·4	8·1
Parsnips	1·60	0·50	13·50	1·40	82·5	19·0
Jerusalem artichokes	2·00	0·50	14·40	1·10	71·8	20·5
Sea-kale	1·40	—	3·80	0·60	21·1	6·0
Turnip	1·30	0·20	8·10	0·80	36·1	12·1
Spinach	2·10	0·30	3·20	2·10	24·4	7·0
Green-peas	7·00	0·50	16·90	1·00	102·7	29·4
Broccoli	3·80	0·30	3·90	0·92	33·2	9·5
Brussels sprouts	1·50	0·10	3·40	1·30	17·9	6·0
Asparagus	1·80	0·20	3·30	0·70	22·7	8·8
Leeks	1·20	0·50	5·80	0·70	23·3	9·9
Green artichokes	4·80	1·70	9·00	1·60	72·4	20·7
Peas (dried)	21·00	1·80	55·40	2·60	329·9	94·1
Lentils (dried)	24·20	1·40	62·40	2·60	368·8	105·2
Sauerkraut	1·40	0·70	2·80	1·70	23·7	6·8
Haricot beans (dried)	23·0	2·30	55·80	3·20	344·4	98·3
Rhubarb	0·60	0·10	1·70	0·50	10·3	2·9
Breads.						
White bread	6·50	1·00	51·20	1·00	245·9	70·4
Brown bread	5·40	1·80	47·10	1·10	229·2	65·5
Graham bread	8·90	1·80	52·10	1·50	265·3	75·8
Hovis	9·90[1]	1·60	42·30	1·20	228·9	65·4
Cytos	8·10[1]	48·30		1·30	231·1	66·2
Manhu	7·20[1]	48·90		1·30	230·0	65·8
Bermaline	8·10[1]	1·70	50·30	1·90	255·2	72·9
Daren	7·90[1]	44·50		1·00	214·9	61·4
Cereals.						
COOKED:						
Rice	0·13	—	16·90	0·10	69·7	19·9
Macaroni	5·60	0·10	27·90	0·20	138·2	39·5
Tapioca	0·60	—	16·60	0·10	70·5	20·1
Scotch oatmeal (water)	3·70	1·80	18·50	1·20	107·7	30·8
Scotch oatmeal (milk)	4·40	2·10	25·90	1·50	143·7	41·1
Quaker oats	1·60	0·30	6·20	0·20	35·3	10·1
Provost oats	2·00	0·40	9·00	0·20	48·0	13·7
Mother's oats	1·90	0·40	8·70	0·20	46·0	13·1
Semolina	1·90	0·10	7·20	0·10	38·3	10·9
Sago	1·40	—	9·30	0·10	44·4	12·7
Vermicelli	2·40	—	10·80	0·10	54·4	15·5
Hominy	2·80	0·10	9·90	0·10	62·8	17·9
Arrowroot	0·30	—	6·10	—	26·2	74·8
Florador	1·80	—	8·70	0·10	43·0	12·3
Farola (fine)	1·80	—	7·80	0·10	40·8	11·7
Granola	2·50	—	9·40	0·20	49·1	14·0
Pearl barley	2·90	0·10	13·10	0·20	55·1	15·8
Oswego	2·90	—	9·70	0·10	51·7	14·8
UNCOOKED:						
Scotch oatmeal	14·60	10·10	65·10	2·10	420·7	120·2
Irish oatmeal	13·40	8·80	68·40	2·00	417·3	119·2
Quaker oats	14·70	6·20	69·80	1·50	404·2	115·5

[1] Protein N × 5·7.

	Protein $N \times 6{\cdot}25$.	*Fat or Ether Extract.*	*Carbo-hydrates.*	*Mineral Matter.*	*Calories in 100 Grammes.*	*Calories in 1 Ounce.*
VEGETABLE FOODS.						
Cereals—UNCOOKED:						
Carter's oats ..	12·90	6·20	76·00	1·80	422·2	130·6
"H—O"	13·80	8·30	67·20	1·70	407·3	116·4
Montgomerie's fine oatmeal	11·00	6·80	74·20	1·70	411·5	117·5
Scot's oat-flour ..	10·00	5·00	77·90	1·30	406·9	116·2
Robinson's groats ..	11·30	6·50	70·40	1·70	396·2	113·0
Rice	5·00	0·10	41·90	0·30	193·2	52·7
Tapioca (foreign) ..	0·00	0·20	86·90	0·00	358·1	102·3
Semolina	11·90	0·60	75·80	0·50	365·5	104·4
Macaroni	10·90	0·60	75·70	0·30	360·6	103·0
Vermicelli	12·50	0·80	75·50	0·30	351·9	100·5
Hominy	8·20	0·60	78·90	0·40	362·6	103·6
Maizena	0·50	—	84·90	0·30	350·2	100·0
Robinson's patent barley	5·10	1·00	81·90	1·90	366·0	104·6
Popcorn	11·20	5·20	71·40	1·40	387·1	110·6
MILK FOODS.						
Milk	87·50	3·50	4·50	0·70	409·5	116·5
Whey	0·80	0·20	4·60	0·60	23·3	6·6
Cream	37·00	22·60	4·20	0·50	242·0	69·1
Cream heavy by centrifugal separator	—	42·00	6·30[1]	—	415·7	119·0
Cream light by centrifugal separator	—	13·80	8·20[1]	—	161·9	46·2
Butter	1·70	85·80	0·20	1·90	805·6	228·9
Butter-milk ..	3·00	0·50	—	4·80	16·8	4·8
Margarine	1·30	82·70	—	6·70	774·8	221·2
Koumiss (alcohol 1·7)[2]	2·20	2·10	1·50	0·90	32·2	10·7
Cheese.						
American	32·90	31·00	—	4·50	422·1	120·1
Bric	18·90	26·80	—	4·50	329·5	94·0
Camembert ..	21·00	21·70	—	4·40	288·1	82·3
Cheddar	33·40	26·80	—	4·30	386·1	110·2
Cheshire	29·40	30·70	—	3·90	405·1	115·6
Cream	8·60	35·90	—	4·30	369·3	105·5
Dutch	30·80	17·80	—	1·50	291·5	83·2
Gloucester	36·70	24·70	—	6·30	380·5	108·8
Gorgonzola.. ..	25·90	26·90	—	4·40	356·5	102·2
Gruyère	31·50	28·20	—	4·70	390·2	111·2
Neuchatel	14·30	43·20	—	1·40	460·6	131·6
Parmesan	43·80	16·50	—	5·90	329·5	94·0
Roquefort	34·80	31·50	—	5·50	435·5	124·5
Stilton	23·90	28·90	—	3·10	459·9	131·2
EGGS.						
Hen's, raw	14·80	10·50	—	1·00	159·5	45·8
,, boiled ..	13·20	12·00	—	0·80	149·9	48·0
,, white, boiled	12·30	0·20	—	0·60	52·1	15·3
,, yolk, boiled ..	15·70	33·30	—	1·10	373·4	106·5
,, white, raw ..	12·60	0·20	—	0·60	53·5	15·6
,, yolk, raw ..	16·20	31·70	—	1·10	361·5	103·4

[1] Solids-not-fat. [2] Alcohol value not included in calories.

	Protein N × 6·25.	*Fat or Ether Extract.*	*Carbo-hydrates.*	*Mineral Matter.*	*Calories in 100 Grammes.*	*Calories in 1 Ounce.*
Egg substitute powders.						
Bird's custard powder	0·60	—	—	0·40	2·3	0·6
Goodall's custard powder	0·60	—	—	0·40	2·3	0·6
Goodall's egg powder[1]	6·00	—	—	2·90	23·6	8·4
Borwick's egg powder[1]	2·90	—	—	—	11·9	3·4
Yeatman's egg powder[1]	6·00	—	—	—	23·6	8·4
Model egg powder ..	5·10	—	—	—	8·2 21·9	2·3 6·2
ARTIFICIAL FOODS.						
Beef extracts, etc.						
Lemco	16·50	—	44·10[2]	21·50	248·6	71·0
Bovril (invalid's) ..	16·50	—	45·30[2]	16·30	261·0	74·3
Bovril	12·20	—	31·70[2]	17·90	180·0	51·4
Brand's essence ..	11·40	—	—	1·40	45·1	12·9
Valentine beef-juice	9·60	—	11·20[2]	10·80	85·3	24·5
Brand's meat-juice	15·40	—	16·50[2]	8·80	139·0	39·1
Lipton's fluid beef	22·10	—	18·70[2]	16·20	167·0	47·0
Burgoyne meat-juice	13·00	—	8·10[2]	14·20	86·4	24·7
Wyeth meat-juice ..	38·00	—	—	17·10	155·1	44·3
Armour's beef-juice	8·30	—	9·50[2]	7·50	73·0	20·5
Puro	30·30	—	19·10[2]	9·70	202·5	57·6
Beef powder.						
Mosquera	77·00	13·00	—	—	323·5	92·3
PATENT FOODS.						
Aleuronat	85·00	—	—	—	—	—
Plasmon	74·10	0·30	7·30	8·50	336·6	96·2
Tilia	76·40	0·10	5·70	9·20	339·1	96·9
Benger's food ..	10·20	1·20	79·50	0·80	378·9	108·3
Benger's food, cooked as directed ..	2·10	2·80	8·20	0·80	66·2	18·9
Mellin's food ..	7·90	—	82·00	3·80	368·7	105·3
Savory and Moore's food	10·30	1·40	83·20	0·60	396·3	113·2
Allenbury's food No. 1..	9·70	20·00	60·80	3·70	475·0	135·7
Allenbury's food No. 2..	9·20	15·00	69·10	3·50	460·6	131·6
FRUITS.						
Apples[3]	0·40	0·50	14·20	0·30	63·3	18·1
Apricots[3]	1·10	—	13·40	0·50	59·5	17·0
Bananas[3]	1·30	0·61	22·00	0·80	101·5	29·0
Blackberries ..	1·30	1·00	10·90	0·50	59·5	17·0
Cherries[3]	1·00	0·80	16·70	0·60	80·5	23·0
Cranberries ..	0·40	0·60	9·90	0·20	46·2	13·2
Figs	1·50	—	18·80	0·60	84·0	24·0
Grapes[3]	1·30	1·60	19·20	0·50	98·3	28·1
Lemons[3]	1·00	0·70	8·50	0·50	45·5	13·0
Nectarines[3]	0·60	—	15·90	0·60	67·2	19·2
Oranges[3]	0·80	0·20	11·60	0·50	52·5	15·0
Pears[3]	0·60	0·50	14·10	0·40	64·4	18·4
Pineapple[3]	0·40	0·30	9·70	0·30	43·4	12·4
Prunes[3]	0·90	—	18·90	0·60	81·5	23·3

[1] All contain baking-soda.
[2] Extractives and non-nitrogenous matter.
[3] Edible portion.

	Protein $N \times 6{\cdot}25$.	*Fat or Ether Extract.*	*Carbo-hydrates.*	*Mineral Matter.*	*Calories in 100 Grammes.*	*Calories in 1 Ounce.*
FRUITS.						
Raspberries[2] ..	1·00	—	12·60	0·60	56·0	16·0
Strawberries[2] ..	1·00	0·60	7·40	0·60	39·2	11·2
Water-melons[2] ..	0·40	0·20	6·70	0·30	31·5	9·0
DRIED :						
Currants (Zante) ..	2·40	1·70	74·20	4·50	325·8	93·1
Figs	4·30	0·30	74·20	2·40	322·0	92·0
Raisins	2·60	3·30	76·10	3·40	350·7	100·2
Dates	2·10	2·80	78·40	1·30	353·5	101·0
NUTS.						
Chestnuts, fresh ..	6·60	8·00	45·20	1·70	286·8	81·9
Peanuts	25·80	38·60	24·40	2·00	560·0	160·0
Walnuts, fresh ..	12·00	31·60	9·40	1·70	381·6	109·0
Filberts, fresh ..	8·00	28·50	11·50	1·50	344·9	98·5
Sweet almonds ..	24·00	54·00	10·00	3·00	641·6	183·3
Cocoanuts, fleshy part	5·20	35·90	8·40	1·00	389·7	111·3
FUNGI.						
Mushroom (*Agaricus campestris*) ..	2·20	0·30	1·20	0·30	16·7	3·3
Chanterelle (*Cantharellus cibarius*) ..	1·20	0·60	5·10	1·20	31·4	8·9
Truffles	6·10	0·60	6·02	2·00	55·2	15·7
Lactarius deliciosus	1·90	0·40	4·50	—	29·9	8·5
Edible boletus ..	3·70	0·54	4·65	—	38·6	11·0
SUGARS AND SWEETMEATS.						
Cane-sugar	—	—	93·30	1·30	382·0	109·1
Beet-sugar	—	—	92·00	2·50	377·0	108·2
Maple-sugar ..	—	—	82·80	—	339·1	96·9
Treacle	—	—	69·70	3·40	285·9	81·8
Honey	1·30	—	73·90	0·10	377·0	108·2
Toffee	—	—	61·00	—	250·0	71·3
Chocolate	12·90	48·70	30·30	2·20	623·1	178·3
Jam (home-made)	—	—	20·00	—	81·9	23·4
Jam (commercial) ..	—	—	30·00	—	122·0	34·9
BEVERAGES.[1]						
Cocoa.						
Fry's pure cocoa ..	19·70	25·60	43·20	5·90	495·6	141·3
Van Houten's cocoa	20·50	28·00	39·70	8·80	507·4	144·9
Epps's prepared	6·70	15·10	71·80	1·50	463·4	132·3
Trinidad nibs cocoa	13·20	50·40	6·30	2·70	547·9	156·6
Coffee.						
Mocha, raw ..	9·90	12·60	10·30	3·70	199·9	57·1
,, roasted ..	11·20	13·60	6·00	4·50	196·9	56·1
East Indian, raw ..	11·20	11·80	9·90	4·00	196·5	56·0
,, roasted	13·10	13·40	1·80	4·90	185·4	51·4
Tea.						
Congou	17·90	—	2·60	6·30	84·1	24·0
Young Hyson ..	17·60	—	3·70	6·10	87·3	24·9
Chinese (cheap black)	22·00	—	—	5·90	90·2	25·7

[1] Sold as dry substance for use.

[2] Edible portion.

	Alcohol by Volume.	*Alcohol by Weight.*	*Protein N × 6.*	*Carbohydrates.*	*Mineral Matter.*
BEVERAGES.					
Beers.	Per Cent.	Gm.			
Bavarian winter ..	3·2	2·5	0·8	3·3	0·2
Bavarian summer ..	3·7	2·9	0·4	5·2	0·2
Munich Hofbrau ..	3·7	2·9	—	—	—
Spatenbrau	3·2	2·5	—	—	—
Pilsener	3·4	2·7	0·4	—	0·2
Munich Bockbier ..	3·4	2·7	0·4	0·9	0·3
English ale and porter ..	4·9	3·9	0·5	0·8	0·3
Berlin white beer ..	3·9	3·1	—	—	—
Allsopp's lager ..	5·4	4·3	0·4	5·4	0·3
Guiness's Dublin stout	5·5	4·4	5·4		0·3
Ciders.					
Devonshire (home-made)	6·0	4·8	1·50[1]		—
Cider	3·4	2·7	8·11		0·3
Champagne perry ..	1·8	1·4	11·01		0·3
Wines.					
Hock (three samples) ..	12·1	9·7	—	0·1	0·2
Claret (three samples) ..	12·1	9·7	—	0·2	0·2
Hungarian wine (three samples)	12·5	10·1	—	0·1	0·2
Greek wine (three samples)	15·4	12·3	—	0·2	0·3
Sherry (three samples)	22·2	17·8	—	3·0	0·5
Madeira (two samples)	22·2	17·8	—	1·8	0·4
Port (three samples) ..	22·6	18·1	—	2·5	0·2
Marsala (two samples)	21·1	16·8	—	3·5	0·3

[1] Solids.

THE PURIN CONTENT OF CERTAIN FOODS.

	Gm. per Kg.
Fish.	
Cod	0·50
Plaice	0·70
Salmon	1·10
Halibut	1·00
Meat.	
Beef	1·10–2·00
Mutton	0·96
Veal	1·10
Pork	1·20
Ham	1·10
Chicken	1·20
Vegetables.	
Potatoes	0·02
Rice	—
Flour	—
Bread	—
Oatmeal	0·53
Peas	0·39
Lentils	0·38
Beans (haricot)	0·63
Asparagus	0·21
Cabbage	—
Lettuce	—
Special Foods.	
Milk	—
Butter	—
Eggs	—
Cheese	—
Beverages.	
Laager beer	0·12
Ale	0·14
Porter	0·15
Tea (methyl-purin), per cup ..	1·20
Cocoa ,, ,, ..	1·00
Chocolate ,, ,, ..	0·70
Coffee ,, ,, ..	1·70
Claret	—
Sherry	—
Brandy	—

INDEX TO VOLS. II. AND III.

By Carey F. Coombs, M.D.

Absorption, blood diseases and, 394
childhood and. See Childhood
cirrhosis of liver and, 276
diabetes insipidus and, 1285
mellitus and, 622
from intestine. See Intestinal absorption
gastric cancer and, 802
motor insufficiency and, 181
secretory disorders and, 178, 180
venous congestion and, 333
gout and, 653
Graves' disease and, 1000
light and, 1214
myxœdema and, 989
obesity and, 705
of fat. See Fat absorption
pancreatic secretory disorders and, 199
renal disease and, 438
Acetanilide and protein metabolism, 1095
Acetic acid, blood diseases and, 392
fermentation in stomach, 185
Aceto-acetic acid. See Acetone bodies, Acidosis, Ketonuria
Acetone bodies in fever, 158
in saliva in diabetes, 621
in starvation, 47
source of, 586
poisoning, glycosuria in, 1098, 1099
Acetonuria, blood diseases and, 392
chloroform and, 1150
epilepsy and, 221
ether and, 1151
Graves' disease and, 1000
nervous diseases and, 1256
obesity and, 711
phosphorus-poisoning and, 1127
Achlorhydria and cancer, 798
and gastric digestion, 171
Acholia, 194, 240
Achylia gastrica, 170 *et seq.*
absorption in, 179
intestinal functions in, 172
urine in, 177
Acidity of urine, chloroform and, 1150
Acidosis in childhood, 861, 882
in diabetes, 597 *et seq.*
mineral waters and, 947
in phlorizin glycosuria, 1196
Acid production in fever, 158
Acids, glycosuria caused by, 1068
Acids, metabolism and influence of, 1066
protein metabolism and, 1068
respiratory exchange and, 1068
Acromegaly, 1017
diabetes and, 565
Acute yellow atrophy, 285
blood in, 293
protein metabolism and, 286
urine in, 287
Addison's disease, 1019
Adrenalin, glycosuria after, 1181
Ahydrochloria and cancer, 798
Alanin excretion in phosphorus-poisoning, 1123
Albumin of blood in renal disease, 497
Albuminates and diabetic glycosuria, 582
Albuminuria, 474
baths and, 976
Bence-Jones, in myelomatosis, 1272
biliary stasis and, 271
blood diseases and, 391
cancer and, 820
carbon monoxide poisoning and, 1092
cardiac diseases and, 342
childhood and, 877
cyclic, 470, 471
diabetes and, 608
diet and, 475
functional, 470, 471
gastric disorders and, 178
gout and, 684
Graves' disease and, 1000
morphine and allied poisons and, 1098
myxœdema and, 988
nervous diseases and, 1255
obesity and, 710
pulmonary diseases and, 342
renal diseases and, 468 *et seq.*
starvation and, 53
Albumose in blood in leuchæmia, 406
in renal disease, 499
Albumosuria, acute yellow atrophy and, 291
burns and, 762
cancer and, 820
cirrhosis of the liver and, 280
gastric disorders and, 178
gout and, 684
infection and, 116
nervous diseases and, 1255
renal disease and, 473
Alcohol, alkalinity of blood and, 1154

Alcohol, diabetic glycosuria and, 582
glycosuria and, 540, 582, 1153
overfeeding and, 64
respiratory exchange and, 1153
uric acid excretion in gout and, 662
Alcoholism, glycosuria in, 540
Alexin of blood, Röntgen rays and, 1226
Alimentary glycosuria. See Glycosuria
lactosuria, 738
lævulosuria, 718. See also Lævulosuria
oxaluria, 1048
pentosuria, 725
toxines in childhood, 850
tract in childhood, 837
in fever, 164, 165
Alkalinity of blood, alcohol and, 1154
alkali ingestion and, 1070
blood diseases and, 410
blood poisons and, 1096
cancer and, 809
cardiac diseases and, 338
chloroform and, 1151
ether and, 1152
fasting and, 32
mineral waters and, 937
obesity and, 708
paraldehyde and, 1152
phosphorus-poisoning and, 1121
pulmonary diseases and, 338
renal disease and, 485
skin diseases and, 772
starvation and, 32
Alkalis, absorption of, in childhood, 860
blood reaction and, 1070
carbohydrate metabolism and, 1074
protein metabolism and, 1072
respiratory exchange and, 1071
urine and, 1074. See also Urine
Alkaptonuria, 1036, 1038
diagnosis, 1043
ochronosis and, 763, 1038
protein metabolism and, 1039
theory, 1039
treatment, 1044
Amido-acids, excretion of, blood diseases and, 386
childhood and, 872
diabetes and, 607
gout and, 681
hot baths and, 970
phosphorus-poisoning and, 1123
renal disease and, 448
in ascitic fluid in Banti's disease, 407
in blood in blood diseases, 407
Ammonia excretion, acute yellow atrophy and, 287
alkalis and, 1075
baths and, 976
blood diseases and, 384
cancer and, 816
cardiac disease and, 342
childhood and, 860
relation to acidosis, 883
cirrhosis of liver and, 278
diabetes mellitus and, 598, 603
gout and, 681
Graves' disease and, 1000, 1002
hot baths and, 970
infection and, 107
Ammonia excretion, mineral waters and, 948
pulmonary diseases and, 342
renal diseases and, 449, 509
skin diseases and, 762
starvation and, 34, 36
of blood in diabetes mellitus, 615
in starvation, 33
Amylene hydrate, 1152
Amyl nitrite poisoning, glycogen loss and, 1096
glycosuria and, 1096
hippuric acid formation and, 1097
lactic acid excretion and, 1096
Anæmia. See Blood diseases, Chlorosis, Hæmorrhage, Pernicious anæmia
Analysis of food-stuffs, 1290
Anilin-poisoning, glycosuria in, 1096
Ankylostomiasis, protein metabolism in, 362
sulphur excretion in, 388
urea excretion in, 383
Antifebrin, 1162
Antimony-poisoning, 1140
Antipyrin, carbohydrate metabolism and, 1162
protein metabolism and, 1095, 1161
respiratory exchange and, 1157
urine and, 1162
Antithyroid serum, 997
Antitoxic function in liver diseases, 296
Appetite in diabetes mellitus, 621
in obesity, 705
Arabinose, 723
Arc-light baths, 1212
Arginin excretion in phosphorus-poisoning, 1124
Aromatic acids, acute yellow atrophy and, 292
blood diseases and, 392
bodies, urinary, in cancer, 818
sulphates, alkalis and, 1076
mineral waters and, 923
skin diseases and, 756
Arsenic in thyroid gland, 1010
poisoning, 1136
Arsenical waters and hæmopoiesis, 936
Arseniuretted hydrogen and alkalinity of blood, 1096
Arthritis deformans, calcium metabolism in, 1269
phosphorus metabolism in, 1269
protein metabolism in, 1263
Assimilation of food in fever, 166
Asthma, dyspeptic, 188
Atony, gastric. See Motor insufficiency
Atrophy, infantile, 886
Atropine, 1179
Autolysis of liver, 290
Azotorrhœa, 202

Bacon, analyses and calorific values, 1290
Bacteria, light and, 1201
motility of, 1205
radium and, 1220
Röntgen rays and, 1220
Banti's disease, amido-acids in ascitic fluid of, 407

Banti's disease, protein metabolism in, 363
purin excretion in, 369
Basedow's disease. See Graves' disease
Baths, albuminuria and, 976
arc-light, 1212
benzol oxidation and, 974
blood and, 978
brine, 972
carbon dioxide, 973
cold, 958
gastric secretion and, 977
glycosuria and, 976
hæmoglobinuria and, 976
heat regulation and, 958 *et seq.*
hot, 965
incandescent, 1211
intestinal secretion and, 977
local effect on metabolism, 977
mud, 974
mustard, 971
radio-active, 974
sea, 972
stimulating, 971
sulphur, 974
sun, 1210
sweat secretion and, 976
tepid, 971
urinary excretion and, 975
Becquerel rays, influence on testes, 1233
Beef, analyses and calorific values, 1290
purin content, 1297
Beer, analyses and calorific values, 1297
purin content, 1297
Bence-Jones albumin in myelomatosis, 1272
Benzoic acid, influence on metabolism, 1173
Bier treatment, 978
Bile acids, acute yellow atrophy and, 293
biliary stasis and, 250, 260
bradycardia and, 262
cholæmia and, 264
hæmolytic action of, 260
bactericidal power of, 197
blood diseases and, 394
fever and, 166
pigment, acute yellow atrophy and, 293
biliary stasis and, 240, 259
cardiac diseases and, 339
fæcal, in childhood, 848
pulmonary diseases and, 339
urinary, in childhood, 875
production in biliary stasis, 239
in cirrhosis of liver, 276
secretion, disorders of, 194
stagnation, 198, 230 *et seq.* See also Jaundice
intestinal functions in, 195, 197
starvation and, 24
Blood, alkalinity of. See Alkalinity
baths and, 978
cholin in, 1253
diseases, absorption in, 394
acetic acid in, 392
acetonuria in, 392
albuminuria in, 391
albumosuria in, 391
amido-acids in, 386
Blood diseases, ammonia excretion in, 384
aromatic acids in, 392
bile in, 394
blood in. See below
chlorides in, 374
creatinin in, 386
digestion in, 393
erythrocytes in. See Erythrocytes
fæces in, 395
fat decomposition in, 398
fat deposition in, 353
fatty acids in, 392
formic acid in, 392
gaseous exchange in, 350
gastric secretion in, 393
glycosuria in, 391
hæmolytic action of serum in, 418
hippuric acid in, 392
indican in, 387
intestinal decomposition in, 399
iron in urine in, 390
lactic acid in, 392
leucin in, 386
mineral metabolism in, 374
nitrogen excretion in, 383
nitrogenous extractives in, 385
nucleo-albuminuria in, 391
nucleo-histone in, 391
oxalic acid in, 392
phenol in, 388
phosphates in, 375
protein metabolism in, 355
ptomaines in, 386
purin bodies in, 365
skin in. See Skin.
sulphates, ethereal, in, 388
sulphur excretion in, 355
tissue chemistry in, 417
toxicity of serum in, 418
tyrosin in, 386
urine in, 381. See also Urine
glycuronic acid in, 728
in acute yellow atrophy, 293
in blood diseases, 400
albumoses of, 406
amido-acids in, 407
chemistry of, 400
dry residue of, 402
fat in, 408
fibrin of, 405
globulins of, 405
glycogen in, 408
minerals in, 410
organic acids in, 409
osmotic concentration of, 400
oxygen capacity of, 416
protein of, 403, 405
decomposition products, 406
specific gravity of, 401
sugar in, 408
uric acid in, 408
xanthin bodies in, 407
in cancer, 805
alkalinity, 809
amylolytic power, 810
chlorides, 810
dry residue, 806

Blood in cancer, hæmolytic power, 810
osmotic pressure, 810
phosphates, 810
proteins, 806
specific gravity, 806
sugar, 810
toxicity, 810
in cardiac disease, 334
in cirrhosis of liver, 277
in diabetes mellitus, 614
insipidus, 1286
in fasting. See Fasting
in fever, 118
in gastric motor disorders, 181
secretory disorders, 176
in gout, 678
in Graves' disease, 1001
in infection, 118
in jaundice, 259
bile acids in, 260
bile pigments in, 259
in myxœdema, 989
in nervous diseases, 1253
in obesity, 706
in osteomalacia, 1271
in pulmonary diseases, 334
in renal disease, 482
albumoses, 499
alkalinity, 485
ammonia, 490
chlorides, 491
concentration, 482
creatin, 491
electrical resistance, 494
fat content, 500
fibrin, 498
"filtrate" nitrogen, 486
freezing-point, 492
morphology, 484
potassium, 491
proteins, 497
purins, 490
serochrome, 499
sugar, 499
toxicity, 494
urea, 486, 489
uric acid, 489
viscosity, 498
in rickets, 1272
in skin diseases, 766
in starvation. See Starvation
intestinal decomposition and, 219
light and, 1212
mineral waters and. See Mineral waters
Röntgen rays and, 1224
uric acid in, in gout, 667, 669
Body-weight in starvation, 20
Borax, 1083
Boric acid, 1083
Bothriocephalus anæmia, absorption in, 396
indican in, 387
protein metabolism in, 361
uric acid excretion in, 367
β-oxybutyric acid. See Acetone bodies, Ketonuria
Bradycardia, bile acids and, 262
Bradyuria, 1283
Breads, analyses and calorific values, 1293
purin content, 1297
Brine baths, 972
Bromides in skin, 786
metabolism and, 1064
Bromine metabolism in nervous diseases, 1255
Bronzing in diabetes, 781
Burns, albumosuria in, 762
erythrocytes in, 767
toxicity of urine in, 764
Butyric acid fermentation in stomach, 185

Cachexia of cancer, 811, 812
Caffeine, 1175
Calcium absorption in childhood, 859
arthritis deformans and, 1269
blood diseases and, 375
excretion in renal disease, 468
in starvation, 44
myxœdema and, 988, 989
osteomalacia and, 1263, 1270
rickets and, 1267, 1270
tetany and, 867
Calculi, urinary, and mineral waters, 944
Calorific values of food-stuffs, 1290
Cancer, 797, 811
achlorhydria in, 798
blood in, 805. See also Blood
cachexia of, 811, 812
digestive processes in, 798
erythrocytes in, 805
experimental data, 824
gastric, absorption in, 802
autolysis in, 801
decomposition processes in, 802
lactic acid in, 802
motility in, 801
hæmoglobin in, 806
intestinal digestion in, 803
leucocytosis in, 808
protein decomposition in, 813
metabolism in, 813
specific factor in metabolism, 820
urine in, 815
acetone bodies in, 819
albumoses in, 820
amido-acids in, 820
ammonia of, 816
aromatic bodies of, 818
chlorides of, 817
lactic acid in, 819
minerals of, 818
nitrogen distribution in, 816
extractives in, 816
peptones in, 820
phosphates in, 817
proteins in, 820
sulphates in, 818
toxicity of, 820
uric acid of, 816
urobilin in, 818
Cane-sugar. See Saccharose
Cantharides-poisoning, 1144
Carbohydrate absorption in childhood, 857
decomposition in stomach, 185
metabolism, alkalis and, 1074
antipyrin and, 1162
fever and, 135, 136

Carbohydrate metabolism, narcotics and hypnotics and, 1147
nervous diseases and, 1251
phosphorus-poisoning and, 1112
thyroid gland and, 1003
Carbohydrates in diabetic urine, 571
Carbolic acid. See Phenol
Carbon dioxide baths, 973
Carbon monoxide poisoning, 1086
albuminuria and, 1092
blood gases in, 1086
glycosuria and, 1091
lactic acid excretion in, 1090
minerals in, 1090
nitrogen excretion in, 1090
protein metabolism and, 1089
respiratory exchange and, 1088
Carcinoma. See Cancer
Cardiac diseases. See Circulatory diseases, Heart
Castration and obesity, 701
Catatonia, energy exchange in, 1245
protein metabolism in, 1248
Cereal foods, analyses and calorific values, 1293, 1294
Cerebro-spinal fluid, cholin in, 1254
pressure of, 1254
protein content of, 1254
Chalybeate waters,
gastric functions and, 917
hæmopoiesis and, 935
Cheese, analyses and calorific values, 1294
purin content, 1297
Chemical composition of tissues in childhood, 834
Childhood, 833
absorption in, 852
acidosis of, 861, 882
alimentary functions in, 837
alkali absorption in, 860
ammonia excretion in, 860
calcium absorption in, 859
carbohydrate absorption in, 857
chloride absorption in, 862
chloride retention in, 868
chlorine deficiency in, 888
energy exchange in, 878
fæces in, 844
fat absorption in, 856
fat excess in, 882 *et seq.*
flesh formation in, 76
food and, 837
disorders of, 882
gastric functions in, 838
hydrochloric acid secretion in, 838
infective diseases of, 881
intestinal decomposition in, 845
processes in, 843
iron absorption in, 868
lactic acid in, 838
liver functions in, 843
mineral absorption in, 857
metabolism of, 867, 874
nitrogen deficiency in, 888
excretion in, 873
nutritional requirements of, 878
pancreas in, 843
pepsin secretion in, 841
phosphorus absorption in, 862
Childhood, protein absorption in, 852
metabolism in, 864
rennet ferment in, 841
respiratory quotient in, 869
saliva in, 838
uric acid infarct of, 878
urine in. See Urine
water absorption in, 868
Chloral hydrate, 1148
Chloralamide, 1148
Chlorates, glycosuria and, 1096
protein metabolism and, 1095
Chlorides, absorption in childhood, 862
deficiency in childhood, 888
in blood diseases, 374, 398, 410, 417
in cancer, in blood, 810
in urine, 817
in childhood, 868, 888
absorption of, 862
nitrogen excretion and, 873
in chloroform narcosis, 1148
in diabetes insipidus, 1287
mellitus, 613
in fever, 163
in Graves' disease, 1001, 1002
in myxœdema, 988
in nervous diseases, 1255
in phosphorus-poisoning, 1128
in pneumonia, 343
in pyrogallol poisoning, 1096
in renal disease, excretion of, 1461 *et seq.*
in blood, 491
œdema and, 464, 492
uræmia and, 466
in skin, 786
in starvation, 40
in syphilis, 765
in toluylenediamine-poisoning, 1096
œdema and, 464, 492
thyroid feeding and, 993, 1002
uræmia and, 466
Chloroform, acetonuria and, 1150
acidity of urine and, 1150
alkalinity of blood and, 1151
bilirubinuria after, 1148
chloride excretion and, 1148
delayed poisoning by, 1151
fatty changes and, 1151
glycosuria after, 1150
phosphorus excretion and, 1148
protein metabolism and, 1148
sulphur excretion and, 1148
urobilinuria after, 1148
Chlorosis, absorption in, 395
blood, dry residue of, 402
iron of, 412
oxygen content of, 416
protein of, 403, 405
specific gravity of, 401
chlorides in, 374
constipation in, 399
gastric acid secretion in, 393
motility in, 181
indican in, 387
intestinal decomposition in, 219, 399
iron of fæces in, 398
phosphates in, 375
protein metabolism in, 363

Chlorosis, respiratory exchange in, 351, 352
urea in, 383
uric acid in, 368
urinary pigments in, 382
Cholæmia, 264
Cholesterin, biliary, 265
Cholin in blood, 1253
in cerebro-spinal fluid, 1254
Chromium poisoning, 1144
Cider, analyses and calorific values, 1297
Circulatory diseases, 304
blood in, 334
digestive organs in, 332
protein metabolism in, 328
respiratory exchange in, 316, 322
quotient in, 323
urine in, 339. See also Urine
Cirrhosis of liver, 272
absorption in, 276
bile secretion in, 276
blood in, 277
gastric functions in, 275
protein metabolism in, 273
urine in, 278
Cocaine, 1177
poisoning, albuminuria in, 1098
glycosuria in, 1098
sarcolactic acid excretion in 1098
Cocoa, analyses and calorific values, 1296
purin content, 1297
Codeïne, 1153
Coffee, analyses and calorific values, 1296
purin content, 1297
Cold baths, 958
heat loss and, 960 *et seq.*
production and, 961
nitrogen excretion and, 964
Coma " casts " in diabetes, 609
diabetic, 597 *et seq.*
Concentration of blood in fasting, 28
in obesity, 706
in starvation, 28
Conductivity, electrical. See Electrical conductivity
Constipation, chlorosis and, 399
gastric secretion and, 172, 176
intestinal decomposition and, 215
motility and, 207
nervous phenomena in, 220
Convalescence, energy exchange in, 68
metabolism during, 168
Copper-poisoning, 1144
Corpuscles. See Erythrocytes, Leucocytes
Creatin of blood in renal disease, 491
uræmia and, 452
Creatinin excretion in blood diseases, 386
in cardiac diseases, 342
in diabetes mellitus, 606
in infection, 108
in pulmonary diseases, 342
in renal disease, 451
in starvation, 38
Cretinism. See Myxœdema
Cryoscopy. See Freezing-point
Curare, 1180
poisoning, albuminuria in, 1098
glycosuria in, 1099
sarcolactic acid excretion in, 1098
Cyanuric acid excretion in phosphorus-poisoning, 1123
Cyclic albuminuria, 470, 471
Cystein, 1022
Cystin in normal metabolism, 1022
Cystinuria, 1021
chronic, 1024
course, 1030
diagnosis, 1031
etiology, 1025
experimental, 1029
phosphorus-poisoning and, 1123
protein metabolism and, 1025
therapeutics, 1030

Decomposition in intestine. See Intestinal decomposition
in stomach, conditions and chemistry of, 185
gastric digestion and, 184
in cancer, 802
intestinal digestion and, 187
metabolism and, 189
nervous system and, 187
Delayed chloroform-poisoning, 1151
Dextrins in urine in diabetes insipidus, 1287
mellitus, 577
Diabète bronzé, 281, 781
Diabetes, 204
absorption in, 622
acromegalic, 565
ammonia excretion in, 598
appetite in, 621
digestive organs in, 620
energy exchange in, 566
fæces in, 622
fat from carbohydrate lessened in, 548
glycogen depots in, 542
Graves' disease and, 1003
insipidus, 1279
blood in, 1286
digestion in, 1285
energy exchange in, 1279
pathogeny of, 1284
protein metabolism in, 1281
sweat secretion in, 1282, 1285
urine in, 1286
water economy in, 1282
intestines in, 622
lævulose utilization in, 546
mellitus, 527
myxœdema and, 1004
pancreatic, 204, 560
glycolytic ferment in blood in, 562
thyroid gland in, 561
protein metabolism in, 569
puncture, 535
renal, 529
saliva in, 620
skin diseases and, 779, 780
stomach in, 621
sugar formation, excessive, in, 550
from fat, 555
from protein, 550
suprarenal, 564
toxic, 536, 537
xanthoma in, 781
xanthosis in, 781

Diabetic acetonuria. See Ketonuria
acidosis, 597 *et seq.*
blood, 614
ammonia in, 615
fat in, 616
ferments in, 616
gases of, 619
glycogen in, 616
hæmolysin in, 616
iron in, 615
potassium in, 615
sodium in, 615
staining reactions of, 618
toxines in, 616
water in, 614
bronzing, 281, 781
coma, 597 *et seq.*
glycosuria, 542. See also Glycosuria
hyperglycæmia, 542
ketonuria. See Ketonuria
urine,
acetone bodies in. See Ketonuria
albuminuria, 608
amido-acids in, 607
ammonia in, 603
cane-sugar in, 573
carbohydrates of, 571
chlorides of, 613
creatinin in, 606
dextrin in, 577
fatty acids in, 610
ferments in, 609
gas in, 612
glucose in. See Glycosuria
glycuronic acid in, 577
hippuric acid in, 606
lactic acid in, 610
lævulose in, 572
maltose in, 574
minerals in, 612
nitrogen in, 603
distribution, 603
"residual," 607
oxalic acid in, 611
pentoses in, 576
phosphates in, 613
purin bodies in, 604
quantity of, 602
specific gravity of, 602
sulphates of, 613
urea in, 603
uric acid in, 604
Diacetic acid in acute yellow atrophy, 288. See also Acidosis, Ketonuria
Diamine poisoning, 1097
Diaminuria, 1032
experimental, 1034
origin, 1033
recognition, 1035
significance, 1035
Diarrhœa, gastric secretion and, 172, 173, 174
intestinal decomposition and, 216
motility of intestine and, 207
Diazo reaction, 162
Diet, albuminuria and, 475
and endogenous obesity, 700
in diabetic ketonuria, 592
in nephritis, 446
Dietetic disorders and skin diseases, 759
Digestion, blood diseases and, 393
cancer and, 798
cardiac diseases and, 332
diabetes insipidus and, 1285
mellitus and, 620
gout and, 651
in intestine. See Intestinal digestion
in stomach. See Gastric digestion
light and, 1214
nervous diseases and, 1252
obesity and, 704
pulmonary diseases and, 332
renal diseases and, 436
Röntgen rays and, 1232, 1233
skin diseases and, 755
starvation and, 22
Dionine, 1153
Dropsy, cardiac, 334. See also Œdema
Drugs and poisons, 1061
Drug tests in renal disease, 481
Dry residue of blood in blood diseases, 402
Ductless glands, diseases of, 983
Dyspeptic asthma, 188
Dyspnœa, compensatory, in oxygen deprivation, 308 *et seq.*
protein metabolism and, 331

Egg powders, analyses and calorific values, 1295
Eggs, analyses and calorific values, 1294
purin content, 1297
Elacin, 783
Electrical conductivity of urine in renal disease, 459
of blood in renal disease, 494
Elimination by intestine, disorders of, 211
Emaciation, cancer and, 811, 812
Endogenous obesity. See Obesity
oxaluria, 1049
Energy exchange, childhood and, 878
convalescence and, 68
diabetes insipidus and, 1279
mellitus and, 566
fasting and, 2
fever and, 120 *et seq.*
gout and, 646
mental diseases and, 1244
mineral waters and, 898, 899
myxœdema and, 984
nervous diseases and, 1244
obesity and, 693 *et seq.*
osteomalacia and, 1261
overfeeding and, 62, 68
rickets and, 1261
Röntgen rays and, 1222
sclerodermia and, 749
skin diseases and, 745, 747
starvation and, 5
water intake and, 898
Enterokinase, 205
Enzymes, light and, 1212
Röntgen rays and, 1222. See also Ferments
Eosinophilia in skin diseases, 770
Epilepsy, acetonuria and, 221
carbohydrate metabolism in, 1251
protein metabolism in, 1247

Erythrocytes in blood diseases, 414
fat of, 414
iron of, 415
minerals of, 415
nitrogen of, 414
oxygen capacity of, 415
weight of, 414
in cancer, 805
in fasting, 28
in renal diseases, 484
in skin diseases, 767
in starvation, 28
Röntgen rays and, 1224
Erythrodermia exfoliativa, nitrogen metabolism in, 747
Ethereal sulphates. See Sulphates, Aromatic sulphates, Indican
Ether narcosis, acetonuria in, 1151
alkalinity of blood in, 1096
glycosuria in, 1098, 1099
protein metabolism in, 1152
respiratory exchange in, 1152
Euglobulin in urine in renal diseases, 470
Exchange of energy. See Energy exchange
Excretion of uric acid, urea, etc. See Uric acid, Urea, etc.
Exophthalmic goitre. See Graves' disease

Fæces in blood diseases, 395
in childhood, 844, 852, 856, 857
fatty acids in, 847
pigments in, 848
in diabetes insipidus, 1285
mellitus, 622
in pancreatic insufficiency, 200
in renal disease, 438
in starvation, 25
Fasting. See Starvation
Fat absorption, bile stagnation and, 195, 196
childhood and, 856
pancreatic insufficiency and, 199
decomposition in blood diseases, 398
excess in diet of childhood, 882 *et seq.*
food and flesh food in overfeeding, 69, 80
from carbohydrate, lessened in diabetes, 548
in blood in blood diseases, 408
in diabetes mellitus, 616
in fasting, 32
in renal disease, 500
in starvation, 32
See also Lipæmia
loss *versus* protein loss in starvation, 19
phosphorus-poisoning and, 1109, 1114, 1117
Fats in skin, 784
Fatty acids in acute yellow atrophy, 288
in blood diseases, 392
in cirrhosis of liver, 279
in fæces in childhood, 847
in jaundice, 269
in urine in diabetes, 610
in skin diseases, 763
change, chloroform and, 1151
phlorizin glycosuria and, 1196
phosphorus and, 1114
Febrile diseases, diabetic glycosuria and, 585
Ferments in diabetes, in blood, 616
in saliva, 620
in urine, 609
in uric acid formation, 656
See also Enzymes
Fever, acetone bodies in, 158
acid formation in, 158
alimentary tract in, 164
assimilation of food in, 166
bile formation in, 165
blood cells, their volume in, 140
carbohydrate metabolism in, 135
chlorides in, 163
energy exchange in, 120
gastric functions in, 164
glycogen metabolism in, 135
"heat centre," puncture of, and, 144
heat loss in, 131
production in, 121, 123 *et seq.*
infective and other forms of, 142
intestinal functions in, 165
liver in, 166
nitrogen secretion in, 107
phosphates in, 163
protein destruction and, 109
respiratory quotient in, 134
saliva in, 164
skin diseases and, 745
water retention in, 139
See also Infection
Fibrin content of blood in renal disease, 498
"Filtrate" nitrogen of blood in renal disease, 486
of œdematous fluid in renal disease, 488
Fish, analyses and calorific values, 1291, 1292
purin content, 1297
Fixed alkalis of urine, ingested alkali and, 1076
Flesh food and fat food in overfeeding, 69, 80
formation in childhood, 76
in convalescence, 77
in lactation, 77
in muscular work, 77
in pregnancy, 77
Food in childhood, 837, 878
disorders due to improper, 882
Food-stuffs, analyses and calorific values, 1290 *et seq.*
purin content, 1297
Formic acid in blood diseases, 392
Freezing-point of blood in renal disease, 492
of gastric juice, mineral waters and, 904
of urine in renal disease, 455, 456, 458
Fructosuria, 716
alimentary, 718
Fruits, analyses and calorific values, 1295, 1296

Galactosuria. See Lactosuria
Gallic acid, protein metabolism and, 1095
uric acid excretion and, 1173
Game, analyses and calorific values, 1291

Gaseous exchange. See Respiratory
Gases of blood in diabetes, 619
Gastric acids in blood diseases, 393
in cancer, 798, 802
cancer. See Cancer
decomposition, influence on digestion, 184 *et seq.*
digestion, cirrhosis of liver and, 275
decomposition in stomach and, 184
motor disorders of stomach and, 180
secretory disorders of stomach and, 170
ferments in cancer, 800
functions, mineral waters and, 904
juice, bactericidal power of, 173
mineral waters and, 904
renal disease and, 437
starvation and, 23
urea in, 438
motility, cancer and, 801
disorders of, 180
blood in, 181
digestion in, 180
intestinal functions in, 181
metabolism and, 183
urine in, 181
secretory disorders of stomach and, 171
secretion, baths and, 977
cancer and, 798
disorders of, 170
absorption and, 178, 180
blood and, 176
gastric digestion and, 170
motility and, 171
intestinal digestion and, 172
metabolism and, 178, 180
pancreatic secretion and, 172
urine in, 176
obesity and, 705
vertigo, 187
Gastro-intestinal lesions and skin diseases, 756
General paralysis, carbohydrate metabolism in, 1251
protein metabolism in, 1247
Glauber's salt, influence on metabolism, 1063
Globulin of blood in renal disease, 498
Globulinuria in renal disease, 469
Glycerin, alkalinity of blood and, 1096
Glycocoll excretion in phosphorus-poisoning, 1123
Glycogen in blood in blood diseases, 408
in diabetes, 616
in diabetes, depots of, 542
in fever, 135
in liver in jaundice, 253
in starvation, 25
in skin, 784
Glycolytic ferment in blood in diabetes, 562
Glycosuria, alimentary, acute yellow atrophy and, 293
alcoholism and, 540
biliary stasis and, 253
cirrhosis of liver and, 281
Glycosuria, alimentary, diabetes insipidus and, 1287
ex amylo, 541
Graves' disease and, 540, 1003
pathological, 538
baths and, 976
hot, 970
blood diseases and, 391
caffeine and, 530
childhood and, 877
diabetes insipidus and, 1287
diabetic, 542
albuminates and, 582
alcohol and, 582
degrees of, 579
febrile diseases and, 585
glycogen depots in, 542
formation and, 547
lactic acid and, 580
lactose and, 575
muscular work and, 582
pentoses and, 576
saccharose and, 573
starches and, 580
sugar unburnt in, 544
variations in, 584
diuretin and, 530
gout and, 683
hyperglycæmia and, 532
hot baths and, 970
ingestion of acetone and, 1098
of acids and, 1068
of adrenalin and, 1181
of alcohol and, 1153
of amyl nitrite and, 1096
of aniline and, 1096
of atropine and, 1179
of carbon monoxide and, 1091, 1098
of chloral hydrate and, 1150
of chloralamide and, 1150
of chlorates and, 1096
of chloroform and, 1150
of cocaine and, 1098
of curare and, 1099
of ether and, 1098
of hydrocyanic acid and, 1107
of morphine and, 1098, 1153
of nitrobenzol and, 1096
of ortho-nitro-phenol-propionic acid and, 1096
of phlorizin (see below), 1183
of strychnine and, 1098
of uranium and, 1143
of veratrine and, 1098
mineral waters and, 955
nervous diseases and, 1251
obesity and, 711
oxygen deprivation and, 327
pathogenesis of, 528
phlorizin, 1183
acidosis in, 1196
cause of, 1183
conditions influencing, 1187
diet and, 1189
dosage and, 1187
fatty change in, 1196
nutrition in, 1194
protein metabolism in, 1192
renal permeability and, 529

Glycosuria, skin diseases and, 763, 779, 780
starvation and, 54
Glycuronic acid, chemistry of, 727
conjugation of, 727, 730
excretion of, 727, 735
in disease, 733
ferments and bacteria and, 730
in blood, 728
in tissues, 728
in urine, 728
diabetic, 577
precursors of, 729, 731
Gonorrhœa, renal functions in, 779
Gout, 646
absorption in, 653
blood in, 678
leucocytes of, 679
molecular concentration of, 679
morphology of, 679
oxalic acid in, 680
specific gravity of, 678
digestive organs in, 651
energy exchange in, 646
hydrochloric acid, gastric, in, 652
indican in, 653
intestinal decomposition in, 653
mineral waters and, 949 *et seq.*
nitrogen retention in, 647
protein metabolism in, 647
renal disease and, 669
saliva in, 652
skin diseases and, 782
theory of, 685
tophi in, 672
uric acid in. See Uric acid
urine in, 680
acidity of, 682
albumin in, 684
albumoses in, 684
amido-acids in, 681
ammonia in, 681
hippuric acid in, 682
minerals of, 682
nitrogen of, 680
oxalic acid in, 683
phosphates of, 682
quantity of, 680
sugar in, 683
sulphates of, 683
urea of, 681
uric acid of. See Uric acid
urobilin in, 682
Graves' disease, 995. See also Thyroid
blood in, 1001
chlorides in, 1001, 1002
diabetes and, 1003
glycosuria in, 540, 1003
phosphorus metabolism in, 1001, 1002
protein metabolism in, 997, 1002
respiratory exchange in, 995
influence of drugs on, 997
sulphur metabolism in, 1001
sweat in, 1001
thyroid feeding and, 1001
urine in. See Urine

Hæmatoporphyrinuria, skin diseases and, 763
Hæmatoporphyrinuria, sulphonal and trional and, 1152
Hæmoglobin, cancer and, 806
fasting and, 28
Röntgen rays and, 1224
starvation and, 28
Hæmoglobinuria, paroxysmal, and baths, 976
skin diseases and, 763
Hæmolysin in blood, diabetes and, 616
Röntgen rays and, 1226
Hæmolysis, bile acids and, 260
Hæmolytic action of blood in cancer, 810
of serum in blood diseases, 418
Hæmophilia, blood in, 420
Hæmopoiesis, arsenical waters and, 936
chalybeate waters and, 935
iron and, 934
Hæmopoietic tissues in infection, 118
Hæmorrhage, ammonia excretion and, 384
chlorides of blood and, 412
of urine and, 374
indican and, 387
oxygen capacity of blood and, 416
phosphates and, 375
protein metabolism and, 355
of blood and, 404
respiratory exchange and, 351
urea excretion and, 383
uric acid excretion and, 366
See also Blood diseases
Hæmorrhagic diseases, skin in, 774
Hæmo-venal salt index, 459
Ham, analyses and calorific values, 1290
purin content, 1297
Heart disease, liver functions in, 333
respiratory exchange in, 322
See also Circulatory diseases
Heat centre, puncture of, and fever, 145
loss, cold baths and, 960 *et seq.*
fever and, 132
production, cold baths and, 961
fever and, 121, 123 *et seq.*
stimulating baths and, 971
regulation, quinine and, 1165, 1166
sweat secretion in skin diseases and, 753
" Hepatic insufficiency," 301
Hepatogenous hyperglycæmia, 535
Hippuric acid, blood diseases and, 392
diabetes mellitus and, 606
gout and, 682
jaundice and, 268
renal disease and, 452
Histone. See Nucleo-histone
Homogentisinic acid, 1036 *et seq.*
tests for, 1043
Hot baths, 965
amido-acid excretion and, 970
ammonia excretion and, 970
phosphate excretion and, 970
protein metabolism and, 969
respiratory exchange and, 965 *et seq.*
Hydræmia in renal disease, 483
Hydrochloric acid, gastric, alkali excretion and, 1079
blood diseases and, 393
cancer and, 798, 802

Hydrochloric acid, gastric, childhood and, 838
diabetes and, 622
gout and, 652
renal disease and, 437
Hydrocyanic acid poisoning, glycosuria in, 1107
lactic acid excretion in, 1107
oxygen deprivation in, 1101, 1105
protein metabolism in, 1107
Hyperchlorhydria, absorption in, 180
gastric digestion and, 170
jaundice and, 238
urine in, 177
Hyperglycæmia, diabetic, 542
glycosuria and, 532
hepatogenous, 535
Hypersthenuria, 458
Hypnotics, 1146
carbohydrate metabolism and, 1147
respiratory exchange and, 1146
Hypochlorhydria and gastric digestion, 171
Hypocholia, 194
Hyposthenuria, 458
Hysteria, protein metabolism in, 1247

Immune substances and nitrogenous metabolism, 94
Incandescent-light baths, 1211
Indican, blood diseases and, 387
childhood and, 847, 875
gout and, 653
Grave's disease and, 1000
test, 212
See also Sulphates, ethereal
Infantile atrophy, 886
scurvy, 889
Infection, 90. See also Fever
albumosuria in, 116
ammonia in, 107
blood in, 118
creatinin in, 108
fever from other causes and, 143
hæmopoietic tissues and, 118
nitrogen excretion in, 107
peptonuria in, 117
protein decomposition in, 100, 115
urea in, 107
uric acid in, 108
Infective diseases in childhood, 881
Inosinic acid, 292
Inosit, diabetes insipidus and, 1287
Inosituria, 743
Internal secretion of kidneys, 497
Intestinal absorption, disorders of, 209
decomposition in intestine and, 217
digestion in intestine and, 209
metabolism and, 210
mineral waters and, 919 *et seq.*
of water, 919
antiseptics, skin diseases and, 757
decomposition, 211
bile stagnation and, 197
blood and, 219
blood diseases and, 399
childhood and, 845
constipation and, 215
Intestinal decomposition, diabetes and, 624
diarrhœa and, 216
gout and, 653
intestinal absorption and, 217
motility and, 215
secretions and, 215
kidneys and, 218, 440
liver and, 218
mineral waters and, 923
muscle and, 219
nervous system and, 220
protein metabolism and, 222
renal disease and, 440
skin diseases and, 219, 756
starvation and, 26
digestion, gastric decomposition and, 187
motor disorders and, 181
secretory disorders and, 172
pancreatic secretory disorders and, 199
diseases, 193
elimination, disorders of, 211
functions in cancer, 803
in childhood, 843
in diabetes, 622
in fever, 165
in jaundice, 237
gases of childhood, 850
motor disorders, 206
intestinal digestion and, 207
metabolism and, 208
secretion, baths and, 977
disorders of, 194
Iodides, alkalinity of blood and, 1096
in skin, 786
metabolism and, 1064
Iodine, alkalinity of blood and, 1096
in thyroid gland, 1006, 1008
metabolism and, 1064
Iodipin, 500
Iodothyrin, 1007
Iron, hæmopoiesis and, 934
in blood diseases, fæcal, 398
hæmatic, 412
tissue, 417
urinary, 390
in blood in diabetes, 615
in childhood, absorption of, 868
influence on metabolism, 1140
Isomaltosuria, 742

Jaundice, 230
albuminuria in, 271
bile acids in, 250
pigment in, 240
production in, 239
blood in, 259
fatty acids in, 269
glycogen content of liver in, 253
glycosuria and, 253
hæmatogenous and hepatogenous, 231
heart disease and, 333
hippuric acid in, 268
hyperchlorhydria and, 238
intestinal processes in, 237
liver functions and, 239
metabolism and, 235

Jaundice, nervous system in, 264
oxalic acid in, 269
protein metabolism in, 235
purins in, 268
sulphur in, 269
sulphuric acid in, 269
uric acid in, 268
urine in, 267

Kairin, 1162
Ketonuria, cancer and, 819
childhood and, 876
diabetic, acidosis and, 597
diet and, 592
its peculiarities, 590
See also Acetonuria, Acetone bodies
Kidneys, internal secretion of, 497
intestinal decomposition, 218, 440
Röntgen rays and, 1233
See also Renal disease

Lachrymal glands, Röntgen rays and, 1233
Lactation, flesh formation in, 77
Lactic acid, acute yellow atrophy and, 290
amyl nitrite and, 1096
arsenic and, 1137
blood diseases and, 392
cancer and, 802, 819
carbon monoxide and, 1090
childhood and, 838
cirrhosis of liver and, 279
diabetic glycosuria and, 580
urine and, 610
fermentation in stomach, 185
gastric cancer and, 802
gastric, in childhood, 838
hydrocyanic acid and, 1107
morphine and, 1098
nervous diseases and, 1256
osteomalacia and, 1272
oxygen deprivation and, 326
Lactose, diabetic glycosuria and, 575
Lactosuria, 575, 737
alimentary, 738
diagnosis, 740
gestation and, 737
in childhood, 877
Lævulose, utilization of, in diabetes, 546
Lævulosuria, 717
alimentary, 539, 718
biliary stasis and, 254
diabetic, 572
diagnosis, 721
etiology, 719
glycosuria and, 717
treatment, 721
Lamb, analyses and calorific values, 1290
Lead-poisoning, 1144
Leuchæmia, albumoses in blood in, 406
ammonia excretion in, 384
chlorides in, 375
dry residue of blood in, 402
indican in, 387
phosphates in, 376
protein metabolism in, 364
of blood in, 404, 405
respiratory exchange in, 351
Röntgen rays and, 1226, 1230
Leuchæmia, skin in, 775
specific gravity of blood in, 401
sulphates in, 388
sulphur metabolism in, 388
urea excretion in, 383
uric acid excretion in, 369, 379
in blood in, 408
xanthin bodies in blood in, 407
in urine in, 372
Leucin, acute yellow atrophy and, 289
blood diseases and, 386
cirrhosis of liver and, 280
phosphorus-poisoning and, 1124
Leucocytes, cancer and, 808
fasting and, 31
gout and, 679
radium and, 1225
renal diseases and, 484
Röntgen rays and, 1225, 1226, 1227
skin diseases and, 769
starvation and, 31
Leucomaines in urine in oxygen deprivation, 328
Lichen planus, nitrogen metabolism in, 754
Light, absorption and, 1214
animals and, 1203, 1205
development of, 1203
organ formation in, 1204
bacteria and, 1201, 1205
blood and, 1212
digestion and, 1214, 1216
enzymes and, 1212
metabolism and, 1199
motor processes and, 1205
penetration of clothing by, 1201
of organic tissues by, 1199
plant life and, 1203, 1205, 1206
protein metabolism and, 1214
protozoa and, 1202, 1205
respiratory exchange and, 1206
sensitization and, 1215
skin and, 1214
Lime. See Calcium
Lipæmia in diabetes, 616
in obesity, 708
See also Fat
Lipolysis in diabetes, 618
Liver, acute yellow atrophy of. See Acute yellow atrophy
antitoxic function in diseases of, 296
cirrhosis of. See Cirrhosis
diseases of, 229
glycogen content in biliary stasis, 253
in biliary stasis, 239
in childhood, 843
in fever, 166
in heart disease, 333
in starvation, 24
intestinal decomposition and, 218
Lymphadenoma. See under Blood diseases, Pseudo-leuchæmia
Lymphocytes in skin diseases, 769

Magnesia. See Magnesium
Magnesium, blood diseases and, 375
osteomalacia and, 1263
rickets and, 1267
starvation and, 44
See also Phosphates

Maltosuria, 740
diabetic, 574
Mast cells in skin diseases, 771
Meat extracts, analyses and calorific values, 1295
Meats, analyses and calorific values, 1290
purin contents, 1297
Mental diseases, 1243
acetonuria in, 1256
albuminuria in, 1255
albumosuria in, 1255
blood in, 1253
bromine excretion in, 1255
carbohydrate metabolism in, 1251
chloride excretion in, 1255
digestive organs in, 1252
energy exchange in, 1245
glycosuria in, 1251
lactic acid excretion in, 1256
phosphorus metabolism in, 1250
protein metabolism in, 1247
uric acid excretion in, 1255
urine in, 1255
toxicity of, 1256
Mercury-poisoning, 1141
Metabolism in acute yellow atrophy. See Acute yellow atrophy
cancer. See Cancer
other diseases. See under respective headings
local effect of baths on, 977
of protein. See Protein
Metallic poisons, protein metabolism and, 1095
Methylpentoses, 725
Milk, absorption of proteins of, 852, 853
analyses and calorific values, 1294
foods, analyses and calorific values, 1294
purin content of, 1297
sugar. See Lactose
Mineral bodies, absorption of, in childhood, 859
excretion of, in blood diseases, 374
in cancer, 818
in carbon monoxide poisoning, 1090
in cardiac disease, 343
in diabetes, 612
in gout, 682
in pulmonary disease, 343
in renal disease, 461
in skin disease, 765
in starvation, 39
mineral waters and, 942
in blood, blood diseases and, 410
metabolism of, in childhood, 867
waters, 897
aerated, 909
alkaline, 910, 914
aromatic sulphates and, 923
bitter, 916
blood and, 929
alkalinity, 937
concentration, 929
formation, 934
osmotic pressure, 931
calcium, 917
calculus formation and, 944
Mineral waters, chalybeate, 917, 935
diabetic acidosis and, 947
energy exchange and, 898
gastric functions and, 904
glycosuria and, 955
intestinal absorption and, 919 *et seq.*
decomposition and, 923
functions and, 918
metabolism and, 897
protein metabolism and, 901
saline, 910, 912
sulphur, 917
urine and, 941
ammonia of, 948
quantity of, 941
minerals of, 942
oxalic acid of, 955
purin bodies of, 949
reaction of, 944
Molecular concentration. See Osmotic pressure
Morphine, albuminuria and, 1098
glycosuria and, 1153
lactic acid excretion and, 1098
protein metabolism and, 1098, 1153
respiratory exchange and, 1153
sarcolactic acid excretion and, 1098
Motor insufficiency of stomach, 180, 183
absorption in, 181
chlorosis and, 181
neuroses of stomach. See Gastric
processes, light and, 1205
Röntgen rays and, 1222
Mucin of myxœdema, 990
Mud baths, 974
Muscular work, diabetic glycosuria and, 582
flesh formation in, 77
Mushrooms, analyses and calorific values, 1296
Mustard baths, 971
Mutton, analyses and calorific values, 1290
purin content of, 1297
Myasthenia, protein metabolism and, 1249
Myeloma, Bence-Jones albumin in, 1272
protein metabolism in, 1263
Myxœdema, 983
absorption in, 989
albuminuria in, 988
blood in, 989
calcium in, 988, 989
chlorides in, 988
diabetes and, 1003
energy exchange in, 984
glycosuria and, 1004
mucin in, 990
nitrogen excretion in, 987
phosphates in, 989
protein metabolism in, 985
respiratory exchange in, 984
sweat in, 988
urine in, 987

Narcotics, 1146
carbohydrate metabolism and, 1147
respiratory exchange and, 1146
Nephritis, acute, diet in, 446
nitrogen excretion in, 442

Nephritis, acute, water excretion in, 453
chronic, diet in, 447
nitrogen excretion in, 443
water excretion in, 454, 455
Nephrolysine, 495
Nervous diseases, 1243
acetonuria in, 1256
albuminuria in, 1255
albumosuria in, 1255
blood in, 1253
carbohydrate metabolism in, 1251
cerebro-spinal fluid in, 1254
digestive organs in, 1252
energy exchange in, 1244
glycosuria in, 1251
phosphorus metabolism in, 1250
protein metabolism in, 1247
urine in, 1255
bromine in, 1255
chlorine in, 1255
lactic acid in, 1256
toxicity of, 1256
uric acid in, 1255
phenomena in constipation, 220
system, biliary stasis and, 264
intestinal decomposition and, 220
Röntgen rays and, 1234
Neutral salts, metabolism and, 1062
Nitrates, alkalinity of blood and, 1096
Nitrobenzol poisoning, glycosuria in, 1096
Nitrogen deficiency in childhood, 888
excretion, acute nephritis and, 442
acute yellow atrophy and, 287, 288
blood diseases and, 383
brine baths and, 972
cancer and, 816
carbon monoxide poisoning and, 1090
cardiac disease and, 340
childhood and, 871
phosphorus excretion and, 874
chronic nephritis and, 443
cirrhosis of liver and, 278
cold baths and, 964
curare and, 1181
diabetes insipidus and, 1286
mellitus and, 603, 607
gout and, 647
Graves' disease and, 1000, 1002
infection and, 101, 107
myxœdema and, 985, 987
obesity and, 709
phosphorus-poisoning and, 1120
pulmonary disease and, 340
renal disease and, 441
Röntgen rays and, 1229, 1230
thyroid feeding and, 993, 1002
via sweat in skin disease, 754
filtrate. See Filtrate
metabolism. See also Protein metabolism
erythrodermia exfoliativa and, 747
immune substance and, 94
lichen planus and, 754
pemphigus and, 753, 754
psoriasis and, 747
skin diseases and, 753
syphilis and, 754
Nitrogen of blood. See Protein of blood
retention in gout, 647
Nitrogen-free food in overfeeding, 69, 80
Nitrogenous excreta in infection, 107
extractives, blood diseases and, 383
cancer and, 816
See also Creatinin, etc.
food in overfeeding, 69, 80
Nuclein katabolism in starvation, 37, 38
Nucleo-albuminuria in blood diseases, 391
in renal disease, 470
Nucleo-histone in blood diseases, 391
Nutrition, cancer and, 811, 812
Nutritional requirements of childhood, 878
Nuts, analyses and calorific values, 1296

Obesity, 693
absorption in, 705
appetite in, 704
blood in, 706
alkalinity of, 708
concentration of, 706
fat in, 708
quantity of, 706
digestive organs in, 704
endogenous (metabolism retarded), 695
daily energy exchange in, 699
diet and, 700
oxygen consumption in, 696
energy exchange in, 693, 699
castration and, 701
thyroid gland and, 701
water restriction in, 702
gastric secretion in, 705
metabolism (normal) and, 694
(retarded) and, 695
protein metabolism in, 703
sebaceous secretion in, 713
thyroid feeding in, 991
urine in, 708
acetone in, 711
albumin in, 710
nitrogen of, 709
oxalic acid in, 711
quantity of, 708
sugar in, 711
uric acid in, 710
water excretion in, 712
Ochronosis, 763
alkaptonuria and, 1038
urine in, 1272
Œdema, chloride retention and, 465, 491, 492
in renal disease, 483, 502
causation of, 502
chloride retention and, 491, 492
filtrate nitrogen and, 488
Oligovaluria, 458
Organic acids of blood in blood diseases, 409
Ortho-nitro-phenol-propionic acid, 1096
Osmotic pressure of blood, blood diseases and, 400
cancer and, 810
diabetes insipidus and, 1286
mineral waters and, 931

Osteomalacia, absorption in, 1270
blood in, 1271
calcium metabolism in, 1263
energy exchange in, 1261
lactic acid in, 1272
magnesium metabolism in, 1263
pathogenesis, 1273
phosphorus metabolism in, 1263
protein metabolism in, 1262
Ovaries, radio-activity and, 1233
Overfeeding, 62
alcohol and, 64
energy exchange in, 62, 68
flesh food and fat food in, 69, 80
Oxalic acid, blood diseases and, 392
distribution in food and body, 1046
excretion, diabetes and, 611
gout and, 683
heart disease and, 325
mineral waters and, 955
jaundice and, 269
in blood in gout, 680
obesity and, 711
origin of, 1048
oxygen deprivation and, 325
Oxaluria, 1046
alimentary, 1048
endogenous, 1049
estimation, 1053
tests, 1053
treatment, 1052
Oxidation processes in blood diseases, 350
Oxybutyric acid, alkalis and, 1076
Oxygen capacity of blood in blood diseases, 415
consumption in endogenous obesity, 696
deprivation, drugs causing, 1084
by action on cells, 1101, 1107
by indirect action, 1098
in diseases of heart and lungs, 304, 305
compensations for, 306, 315
glycosuria and, 327
lactic acid and, 326
oxalic acid and, 325
uric acid and, 325
Oxymandelic acid, 288, 292
Oxyproteic acid in urine, 116
phosphorus-poisoning and, 1123

Pancreas in childhood, 843
Pancreatic diabetes. See Diabetes
secretion, disorders of, carbohydrate in, 199, 203
absorption of fat in, 199, 200
of protein in, 202
fæces in, 200
intestinal digestion in, 199
putrefaction in, 203
metabolism in, 204, 205
gastric secretion and, 172
Paraldehyde, 1152
Paralysis agitans, protein metabolism in, 1248
Patent foods, analyses and calorific values, 1295
Pellagra, 760
Pemphigus, nitrogen metabolism in, 753, 754
Pennyroyal poisoning, 1136
Pentosuria, 722
diabetic glycosuria and, 576
diagnosis of, 725
Pepsin secretion in cancer, 800
in childhood, 841
Peptonuria in acute yellow atrophy, 291
in cirrhosis of liver, 280
in infection, 117
in phosphorus-poisoning, 1123
Pernicious anæmia, absorption in, 395, 396
ammonia in, 384
bilirubin in blood in, 409
chlorides in, 374
dry residue of blood in, 402
gastric hydrochloric acid in, 393
indican in, 387
intestinal decomposition and, 219
oxygen capacity of blood in, 416
pepsin secretion in, 393, 394
phosphates in, 376
protein metabolism in, 360
of blood in, 404, 405
purin excretion in, 368
specific gravity of blood in, 401
sulphur and sulphates in, 388
urea in, 383
uric acid in, 366, 378
urobilin in, 382
See also Blood diseases
Peronine, 1153
Perspiration. See Sweat
Phenol excretion in blood diseases, 388
in childhood, 876
hypotoxic doses and metabolism, 1174
poisoning, glycogen loss in, 1096
Phlorizin, 1183
action on kidneys, 1184
glycosuria, 1183
cause of, 1183
conditions influencing, 1187
nutrition and, 1194
protein metabolism and, 1192
Phosphates, excretion of, alkali ingestion and, 1079
arthritis deformans and, 1269
blood diseases and, 375
cancer and, 817
childhood and, 874
chloroform and, 1148
diabetes insipidus and, 1287
mellitus and, 613
fever and, 164
gout and, 682
Graves' disease and, 1001
thyroid feeding in, 1002
hot baths and, 970
myxœdema and, 989
nervous diseases and, 1250
osteomalacia and, 1263, 1270
phosphorus-poisoning and, 1128
pneumonia and, 343
pulmonary tuberculosis and, 343
renal diseases and, 467
rickets and, 1267, 1270

Phosphates, excretion of, starvation and, 38, 43
in blood in cancer, 810
Phosphatic deposits in skin, 785
Phosphatidrosis, 786
Phosphaturia, 1055
juvenile, 1058
nervous, 1057
physiological, 1056
sexual, 1058
Phosphoric acid. See Phosphates
Phosphorus absorption in childhood, 862
excretion. See Phosphates
and fatty liver, 292
in childhood, nitrogen and, 874
organic, 875
in Graves' disease, 1001
in tissues in blood diseases, 417
Phosphorus-poisoning, acetone excretion in, 1127
alanin excretion in, 1123
alkalinity of blood in, 1121
amido-acids in, 1123, 1125
ammonia excretion in, 1122
arginin excretion in, 1124
carbohydrate metabolism in, 1112
chloride excretion in, 1128
cyanuric acid, excretion in, 1123
cystin excretion in, 1123
fat distribution in, 1115, 1117
fat metabolism in, 1109
glycocoll excretion in, 1123
leucin excretion in, 1124
nitrogen excretion in, 1120
oxyproteic acid excretion in, 1123
peptonuria in, 1123
phosphate excretion in, 1128
protein metabolism in, 1120
respiratory exchange in, 1107
sarcolactic acid in, 1127
sulphate excretion in, 1128
theory of, 1128
tyrosin excretion in, 1124
urea excretion in, 1121
uric acid excretion in, 1122
Pigments in skin, chemistry of, 786
in urine in skin diseases, 763
Pilocarpin, 1177
Plants, influence of light on, 1203
movement in, 1205
radium on, 1221
Röntgen rays on, 1221
Platinum-poisoning, 1144
Pleiocholia, 194
Pleiochromia, 194
Pleurisy, respiratory exchange in, 318, 320
Pneumaturia in diabetes, 612
Pneumonia, albuminuria in, 343
chloride excretion in, 343
phosphate excretion in, 343
protein metabolism in, 330
respiratory exchange in, 317, 323
Poisons and drugs, influence on metabolism, 1061
oxygen deprivation by, 1084
Polycythæmia, splenomegalic, dry residue of blood in, 402
protein of blood in, 404
specific gravity of blood in, 401
Polyvaluria, 458
Pork, analyses and calorific values, 1290
purin content, 1297
Potassium excretion in renal disease, 467
in starvation, 42
in blood in diabetes, 615
in renal disease, 491
Poultry, analyses and calorific values, 1291
purin content, 1297
Pregnancy, flesh formation in, 77
Progressive muscular atrophy, protein metabolism in, 1248
Prostate gland, Röntgen rays and, 1233
Protein absorption in childhood, 852
decomposition, cancer and, 813
fever and, 100, 109
infection and, 100, 109, 116
in stomach, 185
products in blood in blood diseases, 406
digestion, pancreatic insufficiency and, 202
loss *versus* fat loss in starvation, 19
metabolism, acetanilide and, 1095
acute yellow atrophy and, 286
alkalis and, 1072, 1073
alkaptonuria and, 1039
ankylostomiasis and, 362
antifebrin and, 1162
antipyrin and, 1095, 1161
arsenical poisoning and, 1137
arthritis deformans and, 1263
Banti's disease and, 363
biliary stasis and, 235
blood diseases and, 355
bothriocephalus anæmia and, 361
carbon monoxide and, 1089
cardiac diseases and, 328
catatonia and, 1248
childhood and, 864
chloral hydrate and, 1148
chloralamide and, 1148
chlorates and, 1095
chloroform narcosis and, 1148
chlorosis and, 363
cirrhosis of liver and, 273
cystinuria and, 1025
diabetes insipidus and, 1281
mellitus and, 569
dyspnœa and, 331
epilepsy and, 1247
ether and, 1152
fasting and, 7
fever and, 94, 100 *et seq.*
gallic acid and, 1095
general paralysis and, 1247
gout and, 647
Graves' disease and, 997, 1002
hæmorrhage and, 355
heart disease and, 328
hot baths and, 969
hydrocyanic acid poisoning and, 1107
hysteria and, 1247
intestinal decomposition and, 222
jaundice and, 235
leuchæmia and, 364
light and, 1214
mental diseases and, 1247

Protein metabolism, metallic poisons and, 1095
mineral waters and, 901
morphine and, 1098, 1153
myasthenia and, 1249
myelomatosis and, 1263
myxœdema and, 985
nervous diseases and, 1247
obesity and, 703
osteomalacia and, 1262
paraldehyde and, 1152
paralysis agitans and, 1248
pernicious anæmia and, 360
phosphorus-poisoning and, 1120
pilocarpin and, 1178
pneumonia and, 330
progressive muscular atrophy and, 1248
pseudo-hypertrophic muscular palsy and, 1250
pulmonary diseases and, 328
tuberculosis and, 329
pyrodin and, 1095
pyrogallol and, 1095
quinine and, 1166
renal disease and, 434
Röntgen rays and, 1229, 1230
salicyl compounds and, 1095
skin diseases and, 753
starvation and, 13
thallin and, 1162
thyroid feeding and, 991, 1002
toluylenediamine poisoning and, 1095
of blood in blood diseases, 403, 405
in fasting, 28
in renal disease, 497
in skin diseases, 772
in starvation, 28
of urine in starvation, 53
Protozoa, influence of light on, 1202
movement in, 1205
radium on, 1221
Röntgen rays on, 1221
Prussic acid. See Hydrocyanic acid
Pseudo-hypertrophic muscular dystrophy, protein metabolism in, 1250
Pseudo-leuchæmia, Röntgen rays and, 1232
Psoriasis, nitrogen metabolism in, 747
Psychoses, visceral, 221
Ptomaines in intestine, 215
Puncture diabetes, 535
Purin bodies, acute yellow atrophy and, 291
blood diseases and, 385
cardiac disease and, 340
diabetes and, 604
fever and, 108
gout and, 658 *et seq.*
in blood in renal disease, 490
jaundice and, 268
mineral waters and, 949
pulmonary tuberculosis and, 342
renal disease and, 449, 490
Röntgen rays and, 1230, 1231
starvation and, 37
Purin content of various food-stuffs, 1297
Purin-free diet, influence on uric acid excretion in gout, 659
Putrefactive products in intestine, 212, 214, 215
Pyrexia, quinine and, 1165, 1166. See also Fever
Pyrodin, alkalinity of blood and, 1096
protein metabolism and, 1095
Pyrogallol, alkalinity of blood and, 1096
chloride excretion and, 1096
hippuric acid excretion and, 1097
protein metabolism and, 1095
sulphur excretion and, 1096

Quinine in health, 1164
in pyrexia, 1165
protein metabolism and, 1166
respiratory exchange and, 1164, 1165

Radio-active baths, 974
Radium, influence on animals, 1222
on bacteria, 1220
on enzymes and ferments, 1222
on leucocytes, 1225
on ovaries, 1233
on plants, 1221
on protozoa, 1221
on testes, 1233
Red corpuscles. See Erythrocytes
Renal diabetes, 529
disease, 433
absorption in, 438
albuminuria in, 468 *et seq.*
blood in, 482. See also Blood
digestion in, 436
drug tests in, 481
erythrocytes in, 484
fæces in, 438
gastric juice in, 437
globulinuria in, 469
gout and, 669
hydræmia in, 483
intestinal decomposition in, 440
leucocytes in, 484
nephrolysine in, 495
nucleo-albuminuria in, 470
œdema in, 464
protein metabolism in, 434
saliva in, 436
sweat in, 506 *et seq.*
urine in. See Urine
vicarious excretion in, 506
functions in gonorrhœa, 779
in skin diseases, 776, 777
in syphilis, 778
Rennet secretion in cancer, 800
in childhood, 841
Respiratory diseases, 304
blood in, 334
digestion in, 332
protein metabolism in, 328
respiratory exchange in, 316
quotient in, 323
urine in, 339. See also Urine
exchange, alcohol and, 1153
alkalis and, 1071
antipyrin and, 1157
arsenic and, 1137
blood diseases and, 350
carbon monoxide and, 1088
chlorosis and, 351, 352

Respiratory exchange, curare and, 1180
ether and, 1152
Graves' disease and, 995, 997
hæmorrhage and, 350, 351
heart disease and, 322
hot baths and, 965 *et seq.*
leuchæmia and, 351
light and, 1206, 1027
morphine and, 1153
narcotics and hypnotics and, 1146
paraldehyde and, 1152
phosphorus-poisoning and, 1107
pilocarpin and, 1177
pleurisy and, 318, 320
pneumonia and, 317
pulmonary tuberculosis and, 318
quinine and, 1164, 1165
salicylates and, 1172
spectrum colours and, 1209
sunshine and, 1209
vagus section and, 321
Respiratory quotient in cardiac diseases, 323
in childhood, 869
in fever, 134
in pulmonary diseases, 323
"Rhodagen," 997
Rickets, absorption in, 1270
alkalinity of blood in, 1272
calcium metabolism in, 1267
energy exchange in, 1261
magnesium metabolism in, 1267
pathogenesis of, 1273
phosphorus metabolism in, 1267
Röntgen rays, alexin of blood and, 1226
animals and, 1222
bacteria and, 1220
blood and, 1224
energy exchange and, 1222
enzymes and ferments and, 1222
erythrocytes and, 1224, 1226
hæmoglobin and, 1224
hæmolysin of blood and, 1226
kidneys and, 1233
lachrymal glands and, 1233
leucocytes and, 1225, 1226, 1227
leuchæmia and, 1226, 1230
motor processes and, 1222
nervous system and, 1234
nitrogen excretion and, 1229, 1230
nutrition and, 1222
ovaries and, 1233
penetrating power of, 1220
plants and, 1221
prostate gland and, 1233
protein metabolism and, 1229, 1230
protozoa and, 1221
pseudo-leuchæmia and, 1232
purin excretion and, 1230, 1231
salivary glands and, 1233
skin and, 1234
testes and, 1233
thyroid gland and, 1233
uric acid excretion and, 1230, 1231
xanthin bases and, 1232

Saccharose, diabetic glycosuria and, 573
Saccharosuria, 742

Salicyl compounds, 1172
alkalinity of blood and, 1096
protein metabolism and, 1095
Salicylate of soda, uric acid excretion in gout and, 662
Saliva in childhood, 838
in diabetes insipidus, 1285
mellitus, 620
in fever, 164
in gout, 652
in renal disease, 436
urea in, 437
in skin disease, 755
in starvation, 22
Salivary glands, Röntgen rays and, 1233
Sarcolactic acid excretion, acute yellow atrophy and, 288
phosphorus - poisoning and, 1127
various poisons and, 1098
Sausages, analyses and calorific values, 1291
Sclerema neonatorum, 785
Sclerodermia, energy exchange in, 749
Scurvy, infantile, 889
Sea baths, 972
Sebum in obesity, 713
in skin diseases, 784
Secretion of stomach, intestines, pancreas. See Gastric, Intestinal, Pancreatic
theory of thyroid function, 1005, 1010
Sensitization, 1215
biological importance of, 1218
of enzymes, 1216
of infusoria and single cells, 1215
of tissues, 1216
of toxines, 1216
oxygen and, 1217
pathological importance of, 1218
theory of, 1216
therapeutic importance of, 1218
Serochrome of blood in renal disease, 499
Serum, hæmolytic action of, in blood diseases, 418
rashes, 773
toxicity of, in blood diseases, 418
Skin, blood diseases and, 773
chemical changes in, 783
diseases, 745
aromatic sulphates in, 756
blood in, 765
alkalinity of, 772
concentration of, 766
proteins of, 772
diabetes and, 779, 780
dietetic causes of, 759
digestive system in, 755
energy exchange in, 745, 747
eosinophilia in, 770
erythrocytes in, 767
fever and, 745
gastro-intestinal lesions and, 756
glycosuria and, 763, 779, 780
gout and, 782
intestinal antiseptics in, 757
decomposition in, 756
leucocytes in, 769
mast cells in, 771
renal functions in, 776, 777

Skin diseases, saliva in, 755
sweat in, 750
urine in, 761. See also Urine
elacin in, 783
fats in, 784
glycogen in, 784
hæmorrhagic diseases and, 774
halogens in, 786
intestinal decomposition and, 219
leuchæmia and, 775
light and, 1214
minerals in, 785
phosphatic deposits in, 785
pigmentation of, 786
Röntgen rays and, 1234
sebum in, 784
Sodium excretion in starvation, 42
in blood in diabetes, 615
Specific gravity of blood in blood diseases, 401
of serum in blood diseases, 401
Spectrum colours and respiratory exchange, 1209
Splenomegalic polycythæmia. See Polycythæmia
Stagnation of bile, 230 *et seq.* See also Jaundice
Staining reactions of diabetic blood, 618
Starches and diabetic glycosuria, 580
Starvation, bile in, 24
blood in, 28
alkalinity, 32
ammonia, 33
concentration, 28
erythrocytes, 28
fat, 32
hæmoglobin, 28
leucocytes, 31
proteins, 28
sugar, 32
temperature, 33
body-weight in, 20
digestive organs in, 22
energy exchange in, 2, 5
fæces in, 25
fat loss *versus* protein loss in, 19
gastric juice in, 23
glycogen of liver in, 25
intestinal decomposition in, 26
liver functions in, 25
protein metabolism in, 7
saliva in, 22
urine in, 33
acetone bodies, 36, 47
amido-acids, 36
ammonia, 34
calcium, 44
chlorides, 40
creatinin, 38
magnesium, 44
mineral bodies, 39
phosphates, 38, 43
potassium, 42
protein, 53
purins, 37
quantity, 33
reaction, 47
sodium, 42
sugar, 54
Starvation, urine in, sulphur, 46
toxicity, 54
urea, 34
Stimulating baths, 971
heat production and, 971
Stomach, diseases of, 169. See also Gastric
in diabetes, 621
hydrochloric acid secretion, 622
motility, 622
in fever, 164
motility of. See Gastric motility
secretion of. See Gastric secretion
Strychnine-poisoning, 1098
Succus entericus, secretory disorders of, 205
Sugar, defective combustion of, and glycosuria, 544
excess production and diabetes, 550
from fat, 555
from protein, 550
excretion. See Glycosuria
foods, analyses and calorific values, 1296
in blood in blood diseases, 408
in cancer, 810
in fasting, 32
in renal disease, 499
in starvation, 32
in saliva in diabetes, 620
Sulphates, ethereal, in blood diseases, 388
See also Aromatic sulphates, Indican
excretion in alkali ingestion, 1079
in blood diseases, 388
in cancer, 818
in diabetes insipidus, 1287
in diabetes mellitus, 613
in gout, 683
in jaundice, 269
in phosphorus-poisoning, 1128
in renal disease, 466
Sulphocyanides in saliva in diabetes, 620
Sulphonal, 1152
Sulphur baths, 974
excretion, alkalis and, 1075
blood diseases and, 388
childhood and, 875
chloroform and, 1148
pyrogallol and, 1096
starvation and, 46
Graves' disease and, 1001
neutral, blood diseases and, 355
jaundice and, 269
thyroid feeding and, 993
waters and gastric digestion, 917
Sun baths, 1210
Sunshine and respiratory exchange, 1209
Suprarenal diabetes, 564
Sweat, baths and, 976
in diabetes insipidus, 1282, 1285
in gout, uric acid in, 677
in Graves' disease, 1001
in myxœdema, 988
in renal disease, ammonia in, 509
toxines in, 510
urea in, 506
uric acid in, 508

Sweat in skin diseases, 750
clinical data, 751
experimental data, 750
heat regulation and, 753
nitrogen output in, 754
Syphilis, chlorides in, 765
concentration of blood in, 767
erythrocytes in, 767
lymphocytosis in, 769
nitrogen metabolism in, 754
renal functions in, 778

Tea, analyses and calorific values, 1296
purin content, 1297
Temperature of blood in fasting, 33
in starvation, 33
Tepid baths, 971
Testes, effects of radio-activity on, 1233
Tetany, calcium retention in, 867
gastric auto-intoxication and, 188
Thallin, 1162
Theory of gout, 685
Thyreo-globulin, 1006, 1007
Thyroid administration, 991
chlorides in, 993, 1002
Graves' disease and, 1001
metabolism in, 994
nitrogen excretion in, 993, 1002
obesity and, 701, 704
protein metabolism in, 991, 1002
skin diseases and, 749
sulphur in, 993
gland, active substance in, 1006
arsenic in, 1010
carbohydrate metabolism and, 1003
diseases of, 983. See also Graves' disease, Myxœdema
iodine in, 1006, 1008
pancreatic diabetes and, 561
Röntgen rays and, 1233
theories of action of, 1005, 1010
Thyro-iodine, 1006 *et seq.*
Tissues, glycuronic acid in, 728
Toluylenediamine, alkalinity of blood and, 1096
chloride excretion and, 1096
protein metabolism and, 1095
Tophi, gouty, 672
Toxicity of blood in cancer, 810
in diabetes, 616
in renal disease, 494
in skin disease, 772
in uræmia, 494
of serum in blood diseases, 418
of sweat in renal disease, 510
of urine in cancer, 820
in cardiac disease, 344
in pulmonary disease, 344
in renal disease, 480
in skin disease, 763
in starvation, 54
in Weil's disease, 298
Toxines, gastro-intestinal, in childhood, 850
Transformation of energy. See Energy exchange
Trional, 1152
Tuberculosis of lungs, phosphates in, 343
protein metabolism in, 329
purin excretion in, 342
respiratory exchange in, 318
Tyrosin, acute yellow atrophy and, 289
blood diseases and, 386
cirrhosis of liver and, 280
phosphorus-poisoning and, 1124

Underfeeding. See Starvation
Uræmia, 500
alkalinity of blood in, 485
chlorides in, 491
retention of, 466
creatin in, 452, 491
" filtrate " nitrogen of blood in, 487
potassium salts in, 491
toxicity of blood in, 494
urea of blood in, 487, 489
uric acid in, 490
Uranium-poisoning, 1143
Urea excretion in acute yellow atrophy, 287
in blood diseases, 383
in childhood, 872
in cirrhosis of liver, 279
in diabetes insipidus, 1286
in diabetes mellitus, 603
in gout, 681
in Graves' disease, 1000
in infection, 107
in phosphorus-poisoning, 1121
in renal disease, by gastric juice, 438
by saliva, 437
by sweat, 506
by urine, 447
in skin diseases, 761
in starvation, 34, 36
formation in biliary stasis, 256
in blood in renal disease, 486, 489
Urethane, 1152
Uric acid excretion, acute yellow atrophy and, 291
alkalis and, 1075
benzoic acid and, 1173
bothriocephalus anæmia and, 367
cancer and, 816
cardiac disease and, 341
childhood and, 872
chlorosis and, 368
diabetes insipidus and, 1286
diabetes mellitus and, 604
gallic acid and, 1173
gout and, 657, 665, 677, 678
Graves' disease and, 1000, 1002
hæmorrhage and, 366
infection and, 108
jaundice and, 268
leuchæmia and, 369, 379, 1230
mineral waters and, 944, 949
nervous diseases and, 1255
obesity and, 710
oxygen deprivation and, 325
pernicious anæmia and, 366, 378
pulmonary diseases and, 341

Uric acid excretion, renal diseases and, 449
via sweat, 508
Röntgen rays and, 1230, 1231
salicylates and, 1172
skin diseases and, 762
in blood in blood diseases, 408
in gout, 667, 669
in renal disease, 489
infarct of infancy, 878
in gout, 655
deposits of, 672
excretion of, acute attacks and, 665
under ordinary diet, 657
under purin-containing diet, 660, 663
under purin-free diet, 659
via digestive tract, 678
ferments and, 656
in blood, 667, 669, 670
in sweat, 677
purin bases and, 658
sources of, 655
in sweat in gout, 677
in renal disease, 508
Uricæmia of gout, causes of, 670
Urine, acute yellow atrophy and, 287
alkali ingestion and, 1074
ammonia, 1075
aromatic sulphates, 1076
chlorides, 1079
fixed alkalis, 1076
oxybutyric acid, 1076
phosphates, 1079
reaction, 1074
sulphates, 1079
sulphur, 1075
uric acid, 1075
baths and, 975
acidity, 975
albumin, 976
ammonia, 976
lactic acid, 976
minerals, 975
quantity, 975
sugar, 976
biliary stasis and, 267
blood diseases and, 381
acetone, 392
freezing-point, 381
iron, 390
nitrogenous bodies, 383 *et seq.*
pigments, 381
proteins, 391
quantity, 381
reaction, 382
specific gravity, 381
sugar, 391
toxicity, 389
cancer and, 815. See also Cancer
cardiac disease and, 339
albumin, 342
nitrogen, 340
quantity, 339
childhood and, 870
acetone bodies, 876
albumin, 877
amido-acids, 872
Urine, childhood and, bile pigment, 875
indican, 875
nitrogen, 871
phenol, 876
phosphorus, 874, 875
quantity, 871
sugar, 877
sulphur, 875
urea, 872
uric acid, 872, 878
cirrhosis of liver and, 278. See also Cirrhosis
diabetes insipidus and. See Diabetes insipidus
mellitus and. See Diabetic urine
gastric motor disorders and, 181
secretory disorders and, 176
glycuronic acid in, 728
gout and, 680. See also Gout
Graves' disease and, 999
ammonia, 1000
indican, 1000
quantity, 999
urea, 1000
uric acid, 1000
mental diseases and, 1255. See also Mental diseases
toxicity, 1256
mineral waters and, 941. See also Mineral waters
myxœdema and, 987, 988
nervous diseases and, 1255. See also Nervous diseases
toxicity, 1256
obesity and, 708. See also Obesity
ochronosis and colour of, 1272
pulmonary diseases and, 339
albumin, 342
nitrogen, 340
quantity, 339
renal disease and, 441
albumin, 468
albumose, 473
amido-acids, 448
ammonia, 449
calcium, 468
chlorides, 461
creatinin, 451
drugs in, 481
electrical conductivity, 459
euglobulin, 470
freezing-point, 455, 456, 458
globulin, 469
hippuric acid, 452
minerals, 461
nitrogen, 441
nucleo-albumin, 470
phosphates, 467
potassium, 467
purins, 449
quantity, 453
sulphates, 466
toxicity, 480
urea, 447
uric acid, 449
skin diseases and, 761
albumose, 762
ammonia, 762
fatty acids, 763

Urine, skin diseases and, hæmatoporphyrin, 763
hæmoglobin, 763
minerals, 765
pigments, 763
reaction, 761
sugar, 763
toxines, 763
urea, 761
uric acid, 762
starvation and, 33. See also Starvation
Urobilinuria, 241
cancer and, 818
chloroform and, 1148
enterogenous, 245
gout and, 682
hæmatogenous, 243
hepatogenous, 243
histogenetic, 244
nephrogenous, 244
Urolcucic acid, 1037
tests for, 1044
Uroproteic acid. See Oxyproteic acid
Urticaria, 759
blood in, 776

Vagus section, respiratory exchange in, 321
Veal, analyses and calorific values, 1290
purin content, 1297
Vegetables, analyses and calorific values, 1292, 1293
purin content, 1297
Veratrine poisoning, 1098
Veronal, 1152
Vertigo, gastric, 187
Viscosity of blood in cardiac disease, 338
in pulmonary disease, 338
in renal disease, 498

Water absorption from intestine, 919
content of blood in cardiac and pulmonary disease, 334
economy in diabetes insipidus, 1282
excretion, acute nephritis and, 453
obesity and, 712
renal disease and, 453
starvation and, 33, 34
influence on metabolism, 1062
intake, childhood and, 868
concentration of blood and, 929
energy exchange and, 898
restriction in obesity, 702
retention in fever, 139
Waters, mineral. See Mineral waters
Weight of body. See Body-weight
Weil's disease, toxicity of urine in, 298
Weir-Mitchell treatment, 75, 80
Wines, analyses and calorific values, 1297
purin contents, 1297

Xanthin bases, blood diseases and, 398
leuchæmia and, 372
in blood, 407
Röntgen rays and, 1232
Xanthoma diabeticorum, 781
Xanthosis in diabetes, 781
Xylose, 724

Yeast fermentation in stomach, 185

Zinc, influence on metabolism, 1144

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